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OBSERVATIONS ON CORTICAL SOMATIC SENSORY MECHANISMS OF CAT AND MONKEY*

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(Received for publication August 6, 1940)

INTRODUCTION

THE ELECTRICAL RESPONSES of the somatic sensory cortex set up by peripheral stimulation provide one means of studying the phenomena of the local sign. Definite results indicating the applicability of this method to the problem have been reported previously (Gerard, Marshall, and Saul, 1933, 1936; Marshall, Woolsey, and Bard, 1937; Bard, 1938). This paper will deal mainly with certain aspects of the spatial distribution of the cortical reactions set up by stimulation of a single peripheral point and recorded from the pial surfaces of the cat and monkey (*Macaca mulatta*). We place much emphasis on the fact that physiological stimuli in the form of small discrete displacements of hairs or skin were used. Electrical stimulation of peripheral nerves, which cannot be expected to give information of comparable significance for the solution of the problem, was employed only to obtain some complementary data. In addition to an examination of the responses obtained under anesthesia some observations were made on the cortical reactions of unanesthetized animals.

METHODS

Potentials were amplified by a four stage resistance capacity coupled amplifier.‡ The coupling condensers usually used had a capacity of 0.5 microfarad, giving an overall time constant of approximately 93 msec. (see following paper Fig. 1, A, page 28); 4.5 microfarad condensers were available to give a time constant of approximately 0.5 sec. In the later experiments, after consultation with Dr. S. A. Talbot, common mode degeneration having a ratio of 1000 to 1 was introduced into the amplifier. Stimulus occurrence was controlled by a three-channel timing-circuit triggered by a frequency monitor, which also triggered the x-axis unit.

Tactile stimulation was applied to hair-covered areas by a small camel's hair brush, to bare regions by the tip of a short section (about 1–1.5 cm.) of a cat's vibrissa. These objects were mounted on a lever rigidly attached to the moving armature of an electromagnetic device the coils of which were energized by a pulse 3–5 msec. in duration. This produced a regular, quick, to-and-fro movement which, at the end of the lever, amounted to a displacement of approximately 0.5 mm. within a few milliseconds. Arrangements were such that the movement of the stimulator occurred at a given and adjustable point on

* Certain aspects of these observations were previously reported by one of us (Bard, 1938).

† Fellow of National Research Council, 1936–1938, during which time most of these experiments were done.

‡ This amplifier was quite similar to those designed by Mr. Albert Grass for Dr. Hallowell Davis at that time (1936) and was constructed by one of the authors while he was a guest in the laboratory of Dr. Davis. Grateful acknowledgment is made for the helpful advice of Mr. Grass and Dr. Davis.

the x-axis line of the cathode ray tube. Thus a clear signalling of the exact time of activation of the stimulator was assured. The stimulus was repeated at regular intervals of 1 to 2 seconds. Increasing the interval to several seconds had little if any effect on the amplitude of the response. It was found that the application of the stimulator to the skin of a human subject gave a sensation of very light touch which was just above the threshold.

After opening the skull and dura so as to expose the greater portion of the external surfaces of one or both cerebral hemispheres the head of the animal was placed in a Horsley-Clarke instrument constructed to carry two electrodes. This arrangement permitted rapid and precise placing of the leads on the pial surface. In the monkey experiments the cortex was explored by moving the pick-up electrode in steps of one millimeter each along successive antero-posterior and transverse coordinates of the Horsley-Clarke instrument. The positions of the points were also recorded on an enlarged photograph of the brain. Because of the convex contours of the hemisphere the latter is the more accurate way of determining the exact positions and spatial arrangements of the points, but the plotting of an area in terms of coordinates in a horizontal plane is a sufficiently accurate and much more convenient way of arranging the data. In Fig. 2, for instance, the records do not exactly occupy the positions of the points on the brain. The more lateral points are a little more than 1 mm. apart because the mm. readings were taken on a horizontal plane.

In some of the monkey experiments, exploration of one or the other bank of the central sulcus was carried out after the opposing gyrus (precentral or postcentral) had been carefully dissected away. All exposed cortex except the portion under immediate observation was protected from drying by pieces of cellophane.

Nembutal (Abbott's "veterinary") was usually employed for anesthesia. During most of these experiments 0.3 cc. or 0.4 cc. of nembutal was administered whenever the spontaneous activity of the cortex interfered too much with the observation of the correlated response. Some experiments were done on cats and monkeys in which dial, or chlorolosan or ether was used. For each point a picture was taken while observing the cathode ray trace to ascertain whether or not the picture obtained was typical. If a spontaneous wave interfered to any marked extent the record was taken again. Observations under light or no anesthesia were made with the use of an electrode system which could be mounted in trephine holes in the skull. This system consisted of 5 silver wires embedded in bakelite cement* within a short cylinder of stainless steel. The cylinder was threaded at one end so that it could be screwed in trephine holes in a manner similar to that employed by Clark and Ward (1937). The inside diameter of the cylinder was 11.5 mm. The end brought in contact with the cortex presented a smooth surface flush with the ends of the silver wires and these were distributed symmetrically, one in the center and the others equidistant from it on the four quadrant radii. Flexible wires connected each electrode to a switch box and thus any one of the five could be switched into the circuit. Potentials were always measured against the wall of the cylinder which was grounded. The employment of dissimilar metals here is open to some objection. This factor was, however, constant and therefore may be, perhaps, disregarded. Under ether anesthesia two such units were mounted in the skull of the monkey, one on the face or hand area, the other on the trunk or leg area. The skin was loosely sutured around the electrode cylinders and the animal was then secured in a chair in the sitting position. Observations were made on the responses to mechanical and electrical stimuli. The latter were applied through an active electrode of moist cotton twine tied around a toe or digit; the indifferent electrode was attached to the arm or the leg and consisted of a large plate with a saline-soaked gauze pad under it. The electrical stimuli were used to secure more definite information on the absolutely and relatively unresponsive† periods of the reaction than can be obtained with mechanical stimuli. Data on localizations and recovery times were secured, first under ether, next after release of the ether and then for a period of one to two hours under nembutal. During the conscious period the animal appeared to be comfortable and partook liberally of food and drink from the hands of the experimenters.

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* Bakelite cement is probably not suitable for use in chronic preparations, but it appeared to be satisfactory for periods up to 12 hours. These experiments were not conducted over longer periods of time.

† "Unresponsive" is used instead of "refractory" to avoid confusing the phenomena discussed here with the more rigorously defined refractory states of peripheral nerve fibers.

The pick-up electrodes used in experiments on anesthetized animals consisted of moist cotton threads drawn through steel tubing and kept wet with Ringer's solution. A similar arrangement in contact with a silent area or a connection with the Horsley-Clarke instrument served as the indifferent electrode.

Results: Cat

We have found two general types of cortical response. One is the primary response with which these experiments are chiefly concerned. This response, which occurs after a shorter latency than the second type, is definitely localized, predominantly surface positive, often very nearly monophasic, and it repeats very well with each successive stimulus. It is usually the only significant response evoked by weak stimuli when nembutal anesthesia sufficiently deep to reduce considerably or even abolish spontaneous cortical activity is used. The second type of response was investigated briefly in preliminary experiments. There appear to be two kinds of secondary responses. The chief characteristic of the first of these is variability—in shape, phase, latency, and even in incidence of occurrence. Unlike the primary response, it is not always evoked by each successive stimulus and the first phase is not always positive. Detailed observations of it were made in only two cats anesthetized with chlorolosan. The latency appears to be a function of the distance from a region of maximal response for the primary wave. For example, as the electrode was moved caudally along the marginal or suprasylvian gyrus, the latency of the secondary response increased to 3 or 5 times that of the primary response of region 2 for the forefoot (see Fig. 1). The amplitude, incidence, and irregularity of all features of this secondary response increase as the anesthesia becomes lighter.

A secondary response which may be different from that just described sometimes occurs even in deep anesthesia when a peripheral nerve is stimulated by electric shocks. It has not been observed very frequently by us but we are inclined to believe that it resembles the secondary response of Forbes and Morison (1939).

Tactile stimulation of a small area on the dorsal surface of the forefoot consistently evoked at three regions on the surface of the pia of the contralateral cortex (Fig. 1, A and B) potential waves which we believe to be primary responses. Each region showed a maximal response which was usually limited to an area or spot having dimensions less than a millimeter. Occasionally potentials of a comparable order of magnitude were observed over a larger area. For instance, in the animal whose brain is shown in Fig. 1A, there were at region 1 two adjacent spots separated by a short strip from which smaller potentials were recorded. Each region characteristically consists of a maximal spot surrounded by a submaximal margin of variable extent, usually 1 to 2 mm. wide, but not necessarily symmetrical with respect to the maximal point. The two parts of Fig. 1 fairly illustrate the degree of variability found in different preparations.

The potential wave at region 1 was usually the smallest and the most variable; at region 2 the potential was usually larger and more constant; and

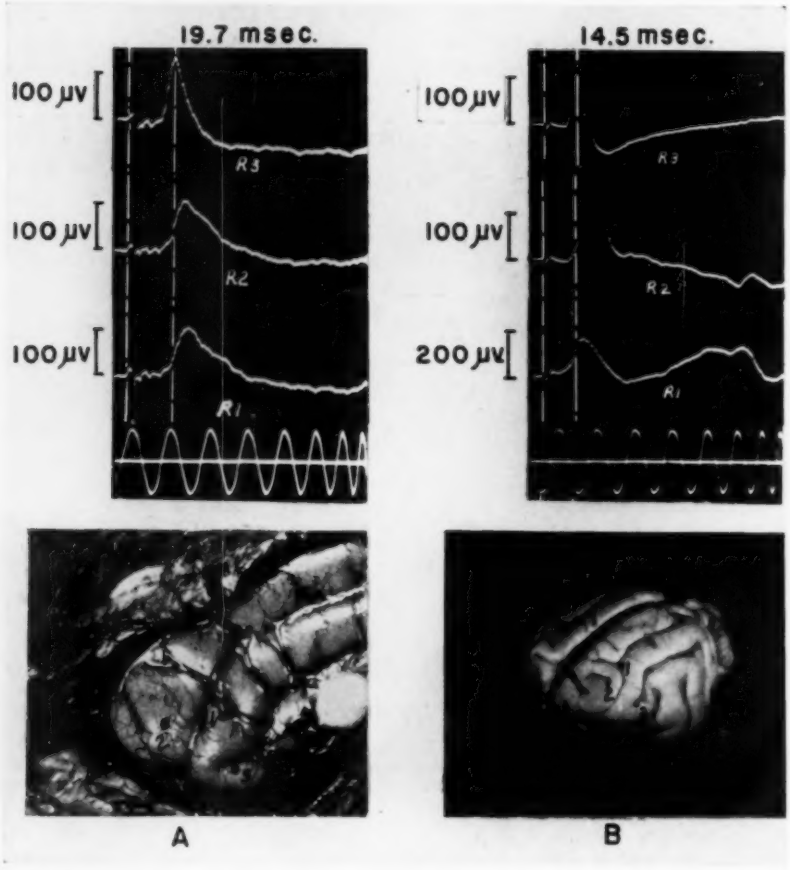


FIG. 1A. Cat, nembutal, 2/19/38. Photograph of rostral pole of left cortex of cat's brain showing regions 1, 2, and 3, and the potential records from each in column above. Stimulus used was camel's hair brush on contralateral forefoot, stimulus sequence in 2 second cycles. In this figure and all subsequent ones electrode positivity is indicated by upward deflection. Vertical lines drawn to show latency differences, and time intervals between them indicated in msec. In these and all subsequent records the mechanical lag of the stimulator is approximately equal to the duration of the signal artifact, so true latencies should be estimated from the end of the stimulus artifact. The time line represents 60 cycles per sec.

B. Cat, nembutal, 3/10/38. Same type of experiment as A. Cortical points marked on a representative picture (brain used in this experiment was not photographed). This example more typical than A in regard to differences of spontaneous activity between region 1 and regions 2 and 3.

at region 3 it was most constant throughout an experiment and showed the shortest latency, highest amplitude and most reproducible wave form. The amplitude of the responses at the three regions varied independently during the course of an experiment. As a rule spontaneous activity was much less at region 3 than at region 1 or 2 (see Fig. 1B). The difference in spontaneous activity varied in different preparations and in different stages of narcosis, but it was usually very definite. Even in quite deep narcosis, the postcruciate

area in which region 2 is located showed stray variations of small amplitude as well as groups of spike-like waves of high amplitude.

Since the tactile stimulator operated with a faint click and because of the proximity of auditory cortex to region 3, it was always necessary in studying the response here to make sure that its source was tactile and not auditory. This was done by the simple process of moving the stimulator away. If the response disappeared it was regarded as somatic; if it persisted and showed increased latency as the stimulator was moved away from the ear, it was assumed to be auditory. In some experiments the tactile response was obtained more caudally on the ectosylvian gyrus than is shown in Fig. 1 and in some cats the region responding to auditory stimuli extends well forward in this gyrus.

In several experiments the question of a primary response to tactile stimulation of the ipsilateral forefoot was investigated. Such a response was found so rarely that it seems reasonable to attribute its occurrence to some experimental error or artifact, expecially in view of the great sensitivity of the contralateral reactions which makes it possible for the application of a slight mechanical stimulus to one side to set up a reaction by stimulating receptors of the other side.

The great sensitivity of these reactions in both cat and monkey demanded considerable care to prevent a slight mechanical stimulus from occurring at other than the desired region in the periphery. For stimulating fixed points in the periphery the tactile stimulating unit was clamped on a heavy stand and the latter was placed on a piece of sponge rubber. The electric cable which connected the stimulating unit to the impulse generator could not be permitted to lie on the table near the animal's body because the barely perceptible vibration imparted to the cable from the movement of the stimulator was transmitted through the table and sometimes stimulated receptors which were in contact with the table. In view of these facts the difficulty of applying proprioceptive or deep pressure stimulation is obvious. There are relatively few muscles that can be completely isolated mechanically so that a stretch stimulus can be applied which will affect that muscle only. If one attempts to excite deep pressure end-organs by placing the wooden lever of the stimulator in contact with some part of the body, the tactile and proprioceptive receptors in a large part of the animal will receive a suprathreshold stimulus. Some of the sources of such artifacts have been revealed only by the masking phenomena (see below). For instance, a weak, and more or less continuous current of air will not usually produce a stimulus sufficiently discontinuous in time to evoke definite surface positive responses of high amplitude, but it may mask the response to the controlled tactile stimulus. Similarly sounds, even those of ordinary conversation, have been observed to mask the response partially or completely. Under certain conditions, opening the camera shutter a fraction of a second before the controlled stimulus occurs produces a tactile stimulus which, depending on the exact time the "click" of the shutter occurs, either sums with the controlled stimulus or partially masks it. This type of artifact could usually be controlled if the camera operator acted as a screen by standing between the camera and the animal. Irregularities in the responses due to respiratory movements were not controlled. For this reason peripheral areas which moved with respiration were not used for securing data discussed in this paper.

It is obvious that in many experiments the actual maximal foci for regions 1 and 3 may have been on the banks of the sulci. Regions lying more than 2 or 3 mm. posterior to the junction of the ansate and lateral sulci were not explored systematically. While no serious attempt was made to map the cat's cortex, as we have done in the case of the monkey, we did devote a few

experiments to an investigation of the general topography of the cat's somatic sensory cortex. The posterior part of the trunk and the hind leg are represented on the medial surface of the hemisphere and on the adjacent portion of the dorsal aspect of the cortex in the region caudal to the cruciate sulcus. The more lateral parts of the post-cruciate region and the regions around the coronal sulcus including the anterior suprasylvian and anterior ectosylvian gyri are concerned with the forelimb, shoulder, neck and face.

The area of cortex from which electrical responses can be recorded when a branch of the superficial radial nerve supplying one or more digits was stimulated by a single induction shock extended over a large part of the frontal pole. The responses to electrical stimuli also showed higher amplitude and shorter latency, than those following physiological (tactile) stimulation.

Monkeys

In one series of experiments the entire Rolandic area of the monkey's brain was mapped by exploring with the tactile stimulator the entire body surface each time the active electrode was placed on a cortical point or spot. It was found that a given cortical spot within the sensory area thus determined may yield potentials of different sizes when a discrete tactile stimulus is applied successively to different points over a restricted peripheral zone on the contralateral side. By determining the relative intensities of these potentials we were able not only to delimit the representation of a part on the cortex, but also to make out with some accuracy the sequence of the representations of different parts and the transitions from one zone to another. The results obtained by this method, together with maps illustrating the topography of the representation of tactile sensibility, have been partially reported elsewhere (Bard, 1938a and b), and will be presented in complete form later. The experiments reported in the present paper had their origin in the observation that tactile stimulation of almost any peripheral point elicits responses over a cortical area of several square millimeters. They deal mainly with measurements of the group or groups of potentials which appear when the stimulation is at a fixed peripheral locus. While the former method is the only practical way of obtaining the necessary information to map the representation of the periphery on the cortex, the latter method gives more accurate information about the manner in which the somatic sensory cortex is activated by stimulation of any one peripheral region.

The points of maximal primary responses

On the basis of anatomical evidence, major reactions should be found in areas 3, 1 and 2 of Brodmann. According to Walker (1938) these are the regions to which the greater part of the radiations from the nucleus ventralis posterior and the nucleus lateralis posterior project. Certain physiological evidence (Bard, 1938a) led us to look for sensory reactions in area 4. We have also investigated areas 5 and 7. The question of ipsilateral representation received considerable attention. Eight experiments on monkeys were devoted principally to plotting out the total cortical area giving electrical responses

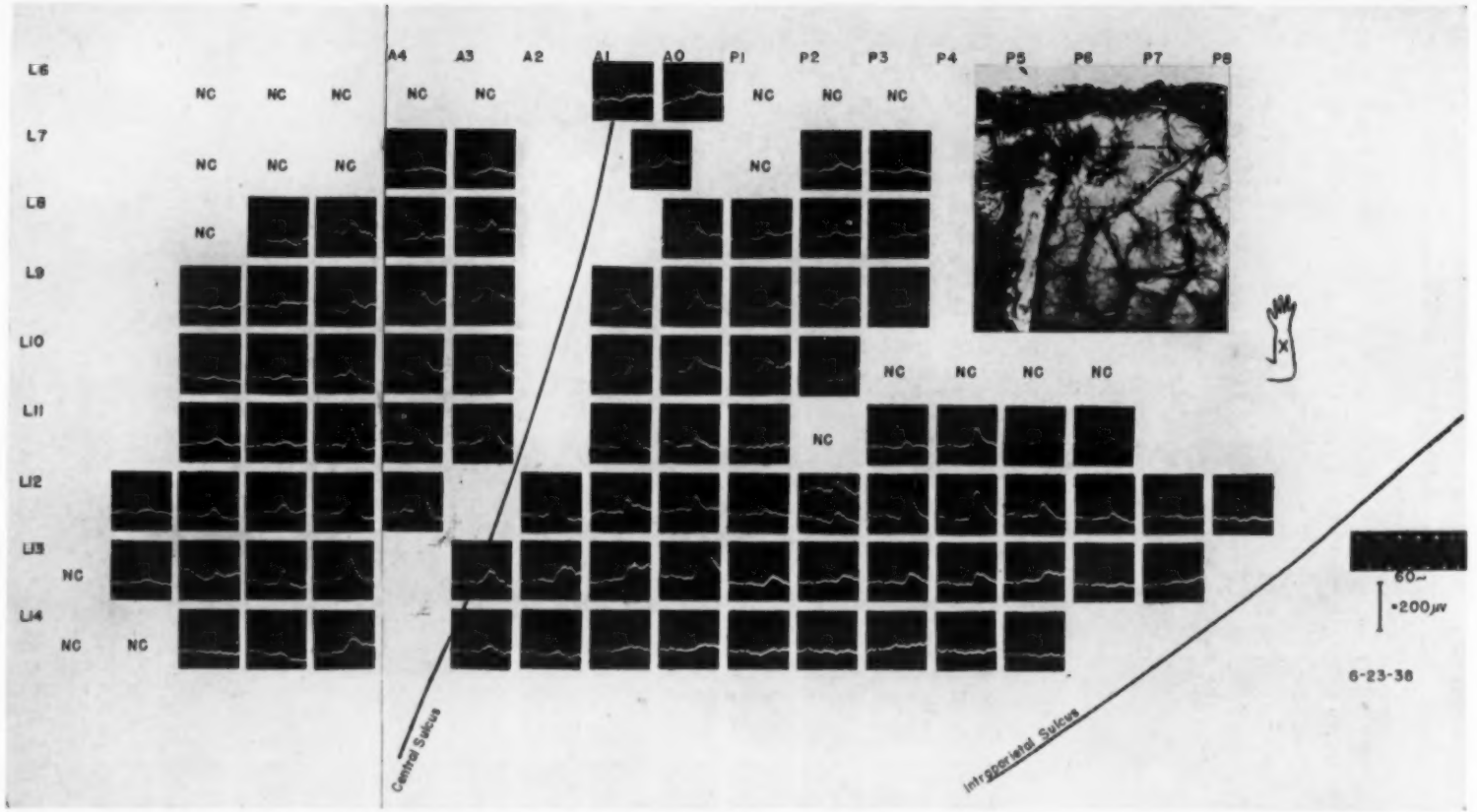
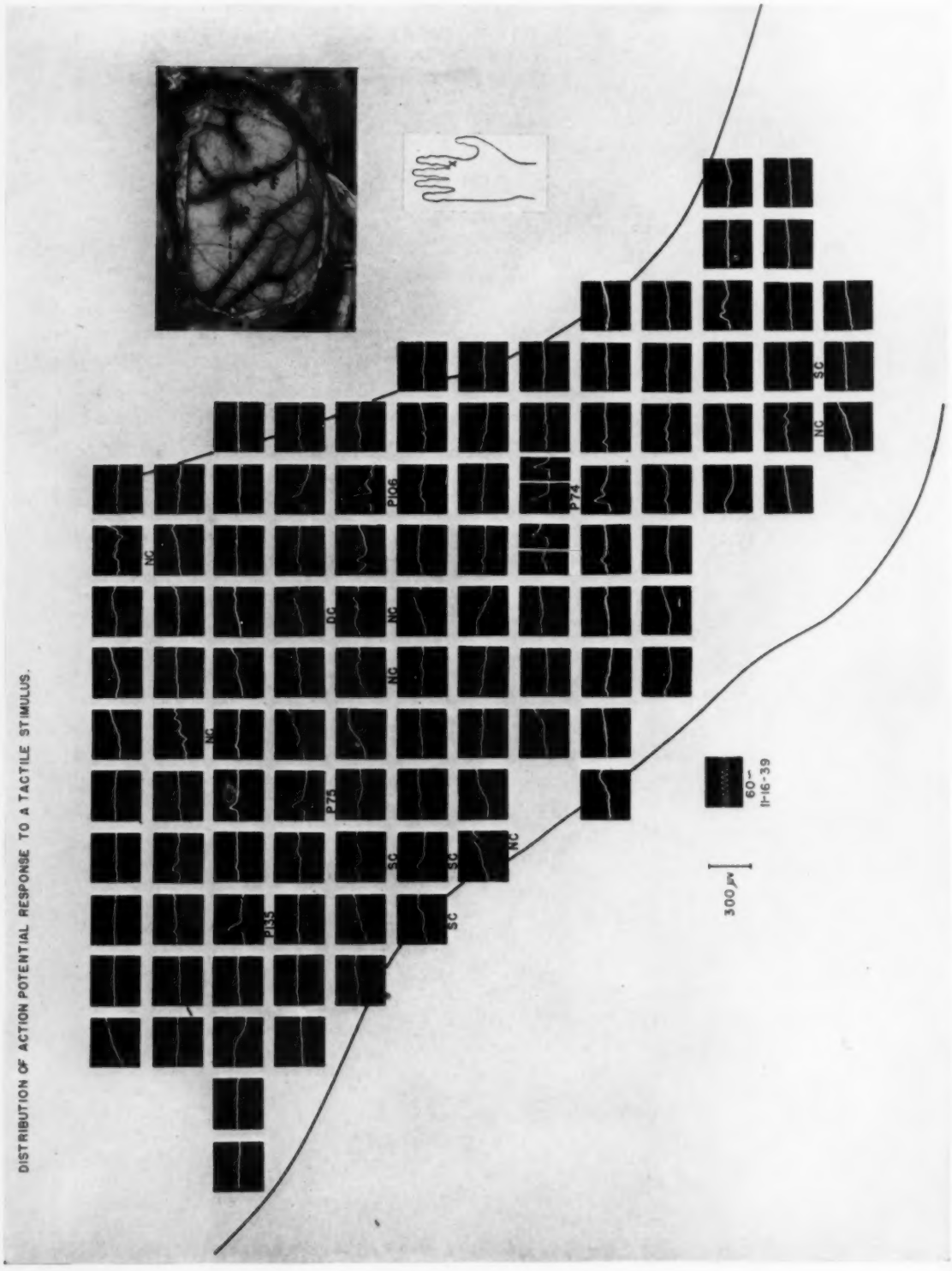


FIG. 2. Monkey, nembutal, 6/23/38. Responses on pial surface of left cortex obtained in response to equal tactile stimuli applied to dorsal surface of right forearm at point X in diagram. Area of cortex surveyed indicated between inked lines on photograph of the brain. Motor cortex removed exposing caudal bank of central sulcus (area 3). Each oscillograph record represents response at a point 1 mm. distant from all adjacent points, as indicated by the mm. coordinates on x (antero-posterior) and y (transverse)axes. Records right of central sulcus line are from dorsal surface of postcentral gyrus. Records at left of central sulcus line taken from rostral bank of postcentral gyrus and, reading to the left, indicate responses at points 1 mm. apart on the bank. Maximal potentials on bank and near rim of central sulcus have latencies of 15 to 16 msec., those at more caudal points show latencies of about 18 msec. NC = no wave correlated with stimulus.


DISTRIBUTION OF ACTION POTENTIAL RESPONSE TO A TACTILE STIMULUS.
P135
P75
P106
P74
NC
DC
SC
300 μv
60~
11-16-39

on stimulation at a fixed peripheral point. All the experiments in this group were done with nembutal anesthesia sufficiently deep to reduce spontaneous activity to a low level, as explained above. The data represent only the primary responses to tactile stimulation.

Some of these experiments were done after exposing the posterior bank of the central sulcus by removal of area 4 by careful subpial dissection. The electrode could then be placed at points on the bank where a significant number of the thalamic neurones terminate (Poliak, 1932; Walker, 1938). An example of such an experiment is illustrated in Fig. 2. In this case light tactile stimulation was delivered by displacement of several hairs on the dorsal surface of the right forearm. The left cortex was explored by moving the pick-up electrode in steps of one millimeter each along successive antero-posterior and transverse coordinates of the Horsley-Clarke instrument. The positions of the points were also recorded on an enlarged photograph of the brain. In this experiment and in several others it was found that maximal potentials occur in three regions within the total area of response. The area of largest potentials was on the posterior bank of the central sulcus and the adjacent dorsal surface (Fig. 2). A second region was found 3 mm. caudal to the sulcus at AO-L13. A third area of maximum potential was found 5 mm. behind the sulcus in the region of P4-L12. The latencies of the reactions near the lip of the sulcus were 12 to 13 msec., while those at the posterior points were 15 msec. The distribution of potentials on the rostral bank of the postcentral convolution was usually similar to that found on the dorsal surface near the rim.

In some experiments the second region of maximal potentials (probably in area 1) was not always clearly set off from the most rostral region, but two regions of maximal response, the one near and in the central sulcus (area 3) and a caudally situated one (probably in area 2) were almost always revealed. The latencies of the responses in the caudal region were always greater than those of the potentials found near the central sulcus.

In the case illustrated in Fig. 3 the rostral bank of the postcentral gyrus was not uncovered, and the records were taken only from the outer surface of the right cortex. A tactile stimulus was applied to hairs on the dorsal surface of the left hand at a point indicated in the diagram. Records were taken at

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FIG. 3. Monkey, nembutal, 11/16/39. Plot of action potential distribution in area of right postcentral gyrus indicated on photograph of brain. Tactile stimulus applied to hairs on back of left hand at point X in diagram. Each oscillogram represents response at a point 1 mm. from adjacent points except at point 74, where 4 oscillograms are shown representing four reproducible responses 0.5 mm. apart. Latency at point 106 was about 13.5 msec.; at point 74, 14 msec.; at point 75, 14.5 msec.; and at point 135, 16 msec. 3 msec. allowed for mechanical lag of the stimulator. During the entire time these records were being taken one channel of a two channel cathode ray system was monitoring a reactive point, either point 74 or point 75, so in no case is absence of response due to general failure of the preparation. An effort was made to get typical pictures unmarred by spontaneous activity and showing only the response correlated with the stimulus. Where the record appears uncertain letters are placed under the record as follows: NC = no correlation, SC = small correlation, DC = dubious correlation.

cortical points 1 mm. apart, except in the region of point 74. Around this point records were taken at 0.5 mm. steps in the antero-posterior direction, and it can be seen how critically the amplitudes of the recorded responses are functions of the electrode position. The assembled data show three principal regions of major reactions, point 74, point 106, and points 75 and 135. The potentials at point 106, which is the one nearest the rim of the central sulcus, showed the highest amplitude and shortest latency (13.5 msec.). The latency of the reaction at point 74 was 14.0 msec., while that at point 75 was 14.5 msec. and that at point 135, 16 msec. A small reaction was found in the lower right corner of the total area of response.

In most of the experiments area 4 was explored, but no definite primary responses were observed either in light or deep anesthesia. Primary responses were occasionally found in the anterior portions of areas 5 and 7, but they were usually weak, and we could never be certain of our ability to repeat the observations with any consistency. Point 135 in Fig. 3, may have been within area 5. Weak reactions were sometimes found at even more posterior points.

The submaximal margin and overlap

Each active region consists of a maximal point surrounded by a submaximal margin 0.5 to 4.0 mm. wide. When the position of the tactile stimulus is moved a short distance the groups of responses are found in slightly different positions, leaving a certain area of overlap. This fact raised the question whether the stimuli at the two peripheral points activate the same neurones within the area of overlap. In attempting to solve this problem we made use of the long and definite unresponsive or absolutely refractory period (25 to 50 msec.) which is exhibited by these reactions under barbiturate anesthesia. Discrete tactile stimuli were applied at two adjacent peripheral points. One stimulus was timed to fall about 25 msec. after the first stimulus, so that, if any neurones were common to both reactions, the ones involved in the first reaction would be in the refractory phase when the second stimulus was delivered and the second response would be correspondingly reduced. As shown in Fig. 4 two separate stimulating units were used to apply tactile stimuli (displacement of hairs) at points on the fourth (D4) and fifth (D5) digits of the left hand. The stimulus, S1, on D4 preceded the stimulus S2, on D5 by 17.5 msec. Since this is within the unresponsive time of these reactions (see below) none of the neurones involved in the D4 reaction will be available for the D5 reaction. Hence, if some part of the D5 reaction is conducted over a pathway independent of the D4 pathway then at some point on the cortex the response evoked from D5 should not be eliminated by the preceding D4 response.

In Fig. 4 the D4 responses appear first on the oscillograph traces. The D5 stimulus occurred at the start of the cortical response to the D4 stimulus. All first waves are D4 responses and where a second wave is present, it represents the fraction of the D5 response recorded from neurones which did not participate in the first reaction. D5 responses of high amplitude are present at

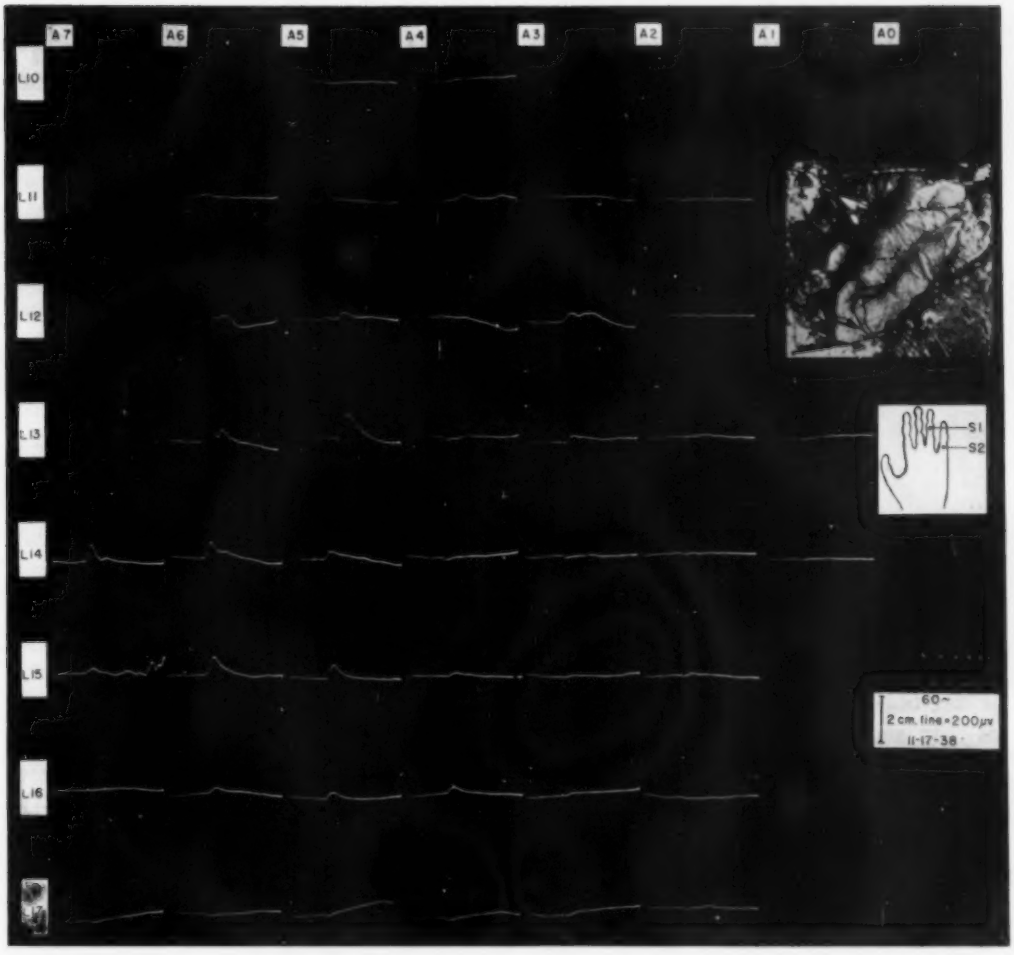

FIG. 4. Monkey, nembutal, 11/17/38. Distribution of action potential responses over area on left postcentral gyrus indicated on photograph of brain. The motor cortex, area 4, had been removed by subpial dissection. Pairs of tactile stimuli were delivered by two camel's hair brush units. First stimulus (S1) at point indicated on digit of right hand and followed after 17.5 msec. by a second stimulus (S2) delivered at the point indicated on digit 5. The stimulus artifacts are not clear on the assembled records. The second stimulus occurred at the start of the wave correlated with the first stimulus. The response to S2 falls within the unresponsive phase of that to S1. At point A6–L13 and at other points, the D4 reaction does not completely abolish the D5 reaction. At A5–L13 the D4 response is near zero and the D5 response is nearly full-sized. The latencies of the two reactions were about the same, 14 msec. for D5 and 13.5 msec. for D4. Each oscillogram was taken at a point 1 mm. from each of the adjacent points.

A6–L12, A6–L13, A6–L14, A5–L13, and A3–L12. The maximal point for both reactions when evoked separately was approximately at A6–L13 and at that point, as well as at most of the others where major responses to either stimulus occurred, the D4 reaction did not completely abolish the other. The exact amount of attenuation was dependent on the strength of the first stim-

ulus and did not indicate any specific separation of the neurones involved. A nearly maximal D5 reaction occurred within the absolutely unresponsive time of the D4 reaction at A5–L13, but at this point the D4 reaction was very small. Other experiments conducted in a similar manner showed the same result. It became clear that a large reaction to the second stimulus occurred only if the electrode was on a point nearly silent for the first reaction, but nearly maximal for the second. In general, this information does not appear to add anything of significant value to that obtained by plotting the distribution of reactions to a single stimulus. It was found that however the attenuating stimulus was arranged in the periphery the maximal reactions are relatively resistant to attenuation.

The experiment illustrated in Fig. 4 is, perhaps, most useful in showing that the almost total absence of the D4 reaction at point A5-L13 was not due to local depression of the cortex at that point, since the D5 reaction was nearly maximal. This result also illustrates the general fact that in areas 3 and 1 cortical spots which do not respond to any peripheral point were rarely encountered.

Another method of demonstrating specific overlap consists in application of the masking effect (Marshall, Woolsey, and Bard, 1937). If continuous tactile stimulation is applied at a point on the periphery near the point at which a discrete tactile stimulus is being applied the specific response to the latter becomes smaller or disappears. In this case the attenuation or abolition of the response is primarily due to equilibration effects, since neurones common to both reactions are kept more or less completely occupied by the continuous stimulation, and at any one time only a few are available for participation in the reaction which follows the discrete stimulus. The long and definite recovery times of these reactions favor the masking effect. Masking can usually be demonstrated wherever overlap occurs. It indicates convergence of central pathways since it can be obtained by stimulating such widely separated peripheral regions as thumb and face which have partially overlapping cortical representations.

The effects of anesthesia

Four experiments were done on monkeys to observe the effects of the anesthetic on the amplitude, latency, recovery time and distribution of the responses. Under ether anesthesia two groups of electrodes, as described above, were screwed into trephine holes in the skull. One electrode group was placed on the postcentral gyrus near the medial rim (foot and leg area), the other just medial to the end of the intraparietal sulcus (face and hand). The animal was then secured in a conventional monkey chair and observations were made from each of the five electrodes of each group while the periphery was explored with the tactile stimulator to find the cutaneous area which was maximally represented under each electrode. These electrodes were theoretically less sensitive to the alpha rhythm than those used in the experiments previously discussed, but their sensitivity to spontaneous activity of beta frequencies was probably about the same.

The evoked responses thus obtained under ether were similar, as regards amplitude and latency, to those obtained in the experiments under nembutal which have been discussed above. They were, however, more difficult to observe because of the much greater spontaneous activity which made precise delimitation of the submaximal margin impossible. A small response under nembutal can be seen distinctly, but the presence or absence of a small

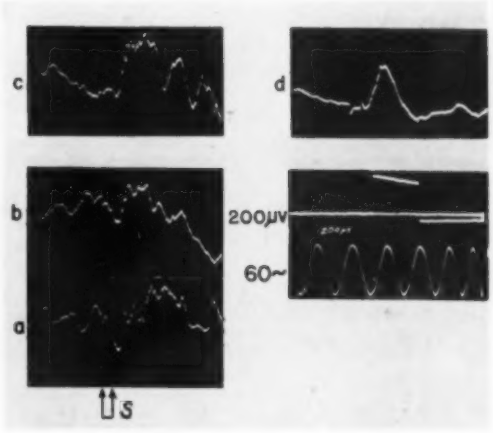

FIG. 5. Monkey, 1/27/38. No anesthesia responses evoked by tactile stimulation of face. Records *a* and *b* show two successive records of response to slight displacement of only two vibrissae. Record *c* shows response to a somewhat stronger stimulus; the camel's hair brush imparted slight movement to several vibrissae. Record *d* taken with approximately same stimulus as for record *c* 3 hours after record *c* was taken and 1 hour after intraperitoneal injection of 0.4 cc. nembutal per kg. S indicates stimulus artifact.

response in the etherized (or the unanesthetized) animal is very difficult to determine. The spontaneous activity under ether could be reduced to an an intensity somewhat comparable to that seen under nembutal only by pushing the anesthesia to dangerous depths. It is perhaps significant that in extremely deep ether anesthesia the responses persisted with about the same amplitude and latency.

After release of ether similar observations were made on the responses to tactile stimulation for periods up to two hours (Fig. 5). In this case also the primary responses were essentially similar to those seen under nembutal, but because of the spontaneous activity it was not so easy to determine the relationship of the wave to the stimulus. In general, the difficulty of observation due to spontaneous activity was less than under ether. The primary surface positive wave was sometimes immediately succeeded by a definite negative wave, and, 10 to 40 msec. later, a second and third diphasic wave sometimes occurred. Each wave in the total response was sharper and contained more small spike-like components than are seen under nembutal or ether. The latencies and amplitudes, however, were about the same as those observed under nembutal.

The extent of the submaximal margin in the unanesthetized animal was, as in the case of ether anesthesia, difficult to determine so we cannot definitely say whether under these conditions the cortical representation of a peripheral point is larger than under nembutal. It appeared, however, to be about the same.

Certain of the above observations as well as the effect of the anesthetics

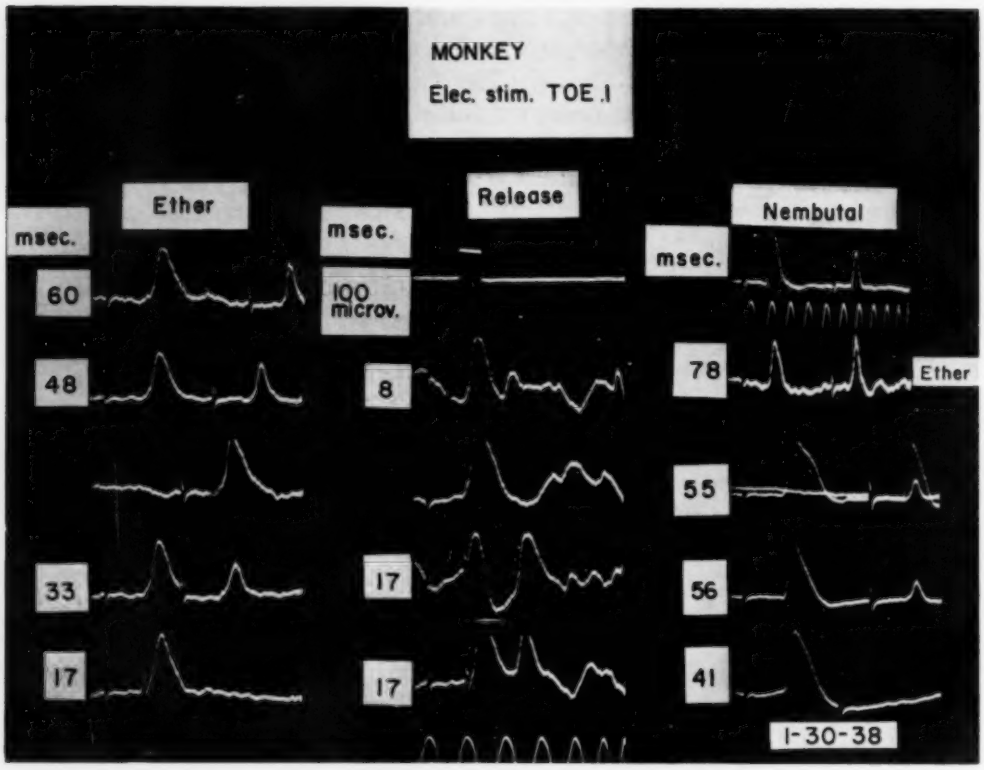

FIG. 6. Monkey, ether-release-nembutal series, 1/30/38. Trephine hole leads on post-central gyrus near central sulcus and close to medial rim of hemisphere. Electric shocks applied to toe I. Records in *column at left* indicate recovery time under deep ether. At 17 msec. second shock produces no response. The third record from the bottom represents control with second shock alone. *Middle column* shows responses obtained 4 to 6 minutes after removal of ether when animal was making spontaneous movements and displayed other signs of consciousness. At 8 msec. interval there is a definite response to second shock. The third record from the bottom represents control in which only the first stimulus was applied. In the *column at the right* the top record (interval 78 msec.) and the three lower records indicate recovery times 12–15 minutes after intraperitoneal administration of nembutal (0.4 cc. per kg.). Record at bottom of column shows interval between stimuli at which second response is near zero. Third record from bottom shows two traces superimposed: the response to a second stimulus after interval of 55 msec. is shown on one and the other represents control in which only the second shock was applied. The two uppermost records of the right column were taken with a slower trace as indicated by the 60 cycles time line between them. Top record was taken about same time as lower three and is to be compared with the ether record below it, which was taken at the same time as the group in the left hand column. Note the difference in size of the second response and the greater amount of spontaneous activity of beta frequency in the ether record.

The latencies of the first response in the ether and nembutal records are practically the same, 17 msec. The latencies after release of ether are about 16.5 msec., a difference of dubious significance. The latencies of the second responses are not significantly different from those of the first responses.

on the recovery time of the reactions can best be illustrated by Fig. 6 and 7. In this experiment, as in the others of this group, observations were made to determine at which electrode tactile stimulation of a digit or toe was maxi-

mally represented while the animal was under ether. Then stimulating electrodes were applied as described above and identical shocks applied in pairs at controllable intervals. The intensity of the shocks was set at a value which gave cortical responses of moderate amplitude with little or no overt reflex or direct muscular movements of the member. These latter complications cannot, however, be definitely excluded.

The recovery times obtained in one of the experiments with the animal first under deep ether anesthesia and later under nembutal are shown in Fig. 6. The records in the right hand column were taken under nembutal two hours after the records in the left hand column had been taken under ether —(all records in the right hand column were taken under nembutal except the one marked "ether"). It is apparent that there are only two obvious differences between the ether and nembutal records. The ether records show more spontaneous activity and a shorter absolutely unresponsive time. It is to be noted that the ether was relatively deeper than the nembutal anesthesia, for, in the monkey, the extent of elimination of spontaneous activity which can be secured by ordinary dosages of nembutal can be obtained under ether only by pushing the anesthesia to a degree not compatible with long maintenance of the preparation. Even so, the recovery time under ether is about one-third that under nembutal. The latter was administered intraperitoneally in a little less than the standard surgical dosage used in this laboratory (0.4 cc. per kg. of body weight).

The records in the middle column of Fig. 6 were taken about 5 minutes after removal of the ether mask and at a time when the animal was making spontaneous movements and showing many signs of consciousness. At this stage and occasionally at longer intervals after release from ether, the recovery times, while much shorter than during the anesthesia, are definitely measurable. In this case, a definite response was obtained when the second stimulus followed the first by 8 msec., and at 17 msec. the second response was about equal to the first. When however, the animal is more completely awake the picture of one simple surface positive response with a long and definite unresponsive time completely disappears. First, the records show more spontaneous activity and then either the refractoriness disappears or a form of summation dominates the refractoriness. The summation effects which often appear at this time are shown in the right hand column of Fig. 7. At 61 msec. they were, in this experiment, pronounced and as the stimulus interval was shortened they became greater. Negative waves and a definite multiple response had not yet appeared when these records were taken approximately 12 minutes after release of ether.

Twenty minutes or more after release of ether the animal eats and drinks from the observer's hands, sometimes vocalizes if he sees food anywhere in the room, exhibits every sign of complete consciousness and appears to be quite confortable. The records taken under these conditions (Fig. 7, left hand column) show more spontaneous activity of both high and low frequency, and the responses to single shocks tend to be multiple. Also summa-

tion occurs, often with the production of definitely diphasic spike-like waves (Fig. 7).

The other experiments of this group did not show such long summation intervals or such prominent multiple responses in the period in which no anesthetics were employed. Typically the summation interval was 15 to 25 msec. long. The summation period was followed by a subnormal phase which

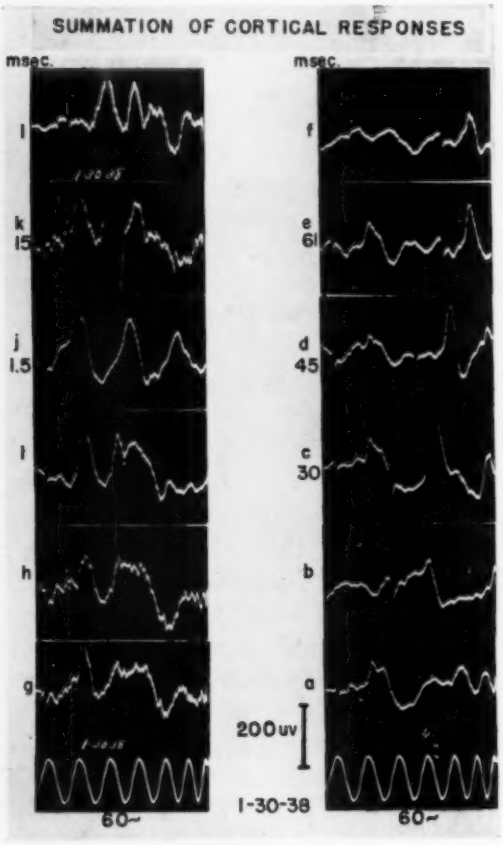

FIG. 7. Monkey, 1/30/38. Same experiment as Fig. 6 and same stimuli, but records taken at longer intervals, after release of ether. Column at right: Records taken 10 to 12 minutes after release of ether. *a* and *b*, 1st and 2nd stimulus alone; in *c* the two stimuli are separated by 30 msec. Note summation or facilitation effect. Records *d* and *e* show this effect at 45 and 61 msec., respectively. Record *f* shows response to second stimulus alone. Note that the summation still exists when the stimuli are separated by 61 msec.

Column at left: Records taken 35 to 40 minutes after release of ether. *g*, *h* and *i* are three successive records showing the degree of variability of the multiple response to a single shock. Record *j* shows the stronger and more reproducible responses resulting from too identical shocks spaced 1.5 msec. apart. Record *k* shows the striking summation effect on the second response of the series when the second shock occurs 15 msec. after the first. While the peaks of the positive and negative phases of the response have not been recorded it is obvious that the positive peak was considerably enhanced and that a strong negative wave has appeared. Record *l* shows control in which only the second stimulus was applied.

Compare these records with those shown in middle column of Fig. 6 which were taken during the same experiment but about 5 minutes after release of ether.

was no longer evident when the interval between the shocks was greater than approximately 30 msec.

DISCUSSION

The potential waves recorded from the cortex on tactile stimulation are believed to be nearly free from artifacts. One objection to the "near" and "remote" lead system is that a strong wave arising anywhere between the electrodes may produce a small potential across them. It was found that with the remote electrode on subcutaneous or muscle tissue over the occiput or on the Horsley-Clarke instrument a small negative wave appeared when the "near" electrode was moved away from the submaximal margin. Thus in the cat a wave such as that from region 3 tends to reduce or deform the response

recorded at region 1 or 2. In the case of tactile stimulation this effect is, however, so small that it may be neglected. On the other hand, with the much stronger reactions from electrical stimulation this lead artifact is large enough to be important. The electrode system we have used is less liable to give error than a "bipolar" system applied to the pial surface. If, for example, one electrode of a "bipolar" system were placed on region 3 and one on region 2 the significant phases of the potentials would be largely cancelled out.

The picture of events recorded from an electrode in the internal capsule (see following paper) suggests several points about the composition of the cortical wave. The spike content of the internal capsule wave is greater or more obvious than that recorded from the pial surface because the electrode is in contact with some of the active fibers; it is probably in effective contact with only a comparatively small fraction of the active thalamo-cortical axons. The pia-arachnoid and probably one or two layers of cortex lie between the cortical electrode and the reacting elements. As Bishop and O'Leary (1936) have pointed out, the tissue between the electrode and the source of activity must, in such a case, be considered part of the electrode. Thus, the "cortical" electrode has considerably larger effective area as regards the nearest responding elements than the electrode in the internal capsule. The branching and horizontal ramifications of the thalamic axon endings in layer IV (Lorente de Nó, 1938) must also contribute to a smoothing of the slow component. Recent observations have shown that electrical stimulation of the lemniscus produces a cortical response composed of two surface positive spikes of axon dimensions followed by a positive wave 3 to 5 msec. in duration. This is comparable to the reaction described by Bishop and O'Leary (1938) for the optic cortex. Presumably, the cortical response to peripheral stimulation is due to simple addition of complexes such as these which are temporally dispersed. The fact that the duration of the wave in the internal capsule is about the same as that of the primary cortical response (see Fig. 1, 2, and 4 of the following paper) indicates that the positive cortical wave observed in nembutal anesthesia approximately coincides with the bombardment over thalamo-cortical neurones. The rates of rise and fall of the two waves are also similar.

We recognize three types of cortical responses to peripheral stimulation: the primary cortical response and two varieties of secondary response. The primary response is always initially surface positive and with strong stimulation it is typically followed by a negative wave of small amplitude and long duration (Fig. 8) which may represent a positive after-potential inverted in recording. The primary response is the most highly localized, has the shortest latency, and is very reproducible. The first type of secondary response is quite variable and has been observed in detail in cats under light chlorolosan anesthesia. This type of secondary response occurs only when spontaneous cortical activity is present and is somewhat similar to the secondary reactions described by Adrian and Moruzzi (1939). The second type of secondary

response (apparently similar to that described by Forbes and Morison, 1939) is more reproducible and has a longer latency, but we have only occasionally seen it. It is seen only when spontaneous cortical activity is small or absent. Its absence in our experiments is probably due to the fact that practically all our observations were made under the conditions of equilibration which exist at a cycle frequency of 1 to $\frac{1}{4}$ per second. According to the data of Forbes and Morison the recovery time of this type of secondary response might tend to prevent its appearance when the reaction is equilibrated at these frequencies.

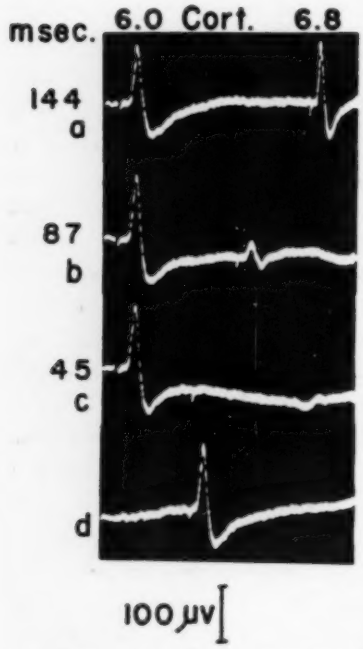

FIG. 8. Cat, nembutal 3/23/38. Same experiment as illustrated in Fig. 4 of following paper. Cortical responses at region 3 to two electric shocks applied to superficial radial nerve at intervals indicated at left of records. Stimulus cycle, 4 seconds. Latencies are indicated over 1st and 2nd responses. Note that second response is maximal at a stimulus interval of 144 msec. and nearly zero at one of 45 msec. Record *d* shows control in which second stimulus was applied alone.

Whether or not the primary response of Forbes and Morison (1939) is essentially the same as the primary response considered here has been questioned (Forbes and Morison, 1939, pp. 122–133) on the basis of the relation of frequency of stimulation to response amplitude. In a previous paper (1937) we stated that with mechanical stimulation of hairs the response disappeared, *i.e.*, was no longer visible on the oscillograph trace, at a frequency of 12 to 15 per second. Mechanical stimulation as used by us, is not a satisfactory method for the study of either recovery times or equilibration and fatigue effects, since at these frequencies the vibrating brush does not apply a temporally discrete stimulus. The values obtained with this method of stimulating are undoubtedly too low, and therefore electrical shocks to peripheral nerve trunks were principally used in the investigation of recovery times (see the following paper).

Forbes and Morison found that, at a stimulation frequency of 7 per second (electrical shocks applied to the sciatic nerve) the amplitude of their primary cortical response in the cat under nembutal was more than half the initial amplitude, and on this basis they argue that the response should not decline to extinction at double that frequency. Forbes and Morison, however, cite values obtained under conditions of equilibration and these values do not give definite information about the absolutely and relatively unresponsive periods because the reaction merely fractionates as the stimulus frequency is increased and eventually becomes invisible on the oscillograph. We therefore wish to refer to an experiment on a cat under nembutal which

illustrates the extent of the reduction of the response to the second of a pair of stimuli as the interval is progressively decreased. In this experiment the pairs of stimuli were electrical shocks applied to the superficial radial nerve at a cycle frequency of $\frac{1}{4}$ per sec. (1 cycle in 4 sec.). The shocks were stronger than necessary to produce a maximal cortical reaction. At an interval of 144 msec. (equivalent to a frequency of 7 per sec., disregarding fatigue effects) the response was full sized (Fig. 8a). At an interval of 87 msec. (equivalent to a frequency of 11.5 per second, if we disregard equilibration) the second response was very much reduced (Fig. 8b) and at 45 msec. (equivalent to a frequency of 22 per sec., disregarding equilibration) it was barely discernible (Fig. 8c). It is clear that as the stimulus intervals are shortened to bring the second stimulus progressively further into the relative recovery time the response rapidly decreases. Equilibration at frequencies equivalent to these intervals yields amplitudes for each wave which are somewhat greater than those shown for the respective second responses, but it appears that the actual amplitude at any given frequency is that which can be predicted from simple fractionation plus possible fatigue effects. These considerations indicate that the individual responses should rapidly decrease as the stimulus frequency is increased above 7 per second.

In all of our experiments the primary foci were carefully located by restricted physiological stimulation before determinations of recovery time or other observations on responses to electrical stimulation were made. The positions of the maximal potentials evoked by electrical stimulation of the superficial radial nerve do not always exactly coincide with the positions determined by physiological stimulation, but they are always very near one another. When electrical shocks are used some potential complex can be picked up almost anywhere on the frontal pole of the cat's brain. Some part of this potential is lead artifact and part of it is still observed when differential leads are used. It is obvious that placing the active electrode on or near one of the maximal spots greatly reduces the probability of observing side chain reactions (avalanche conduction) which are recruited in significant numbers through any synaptic region when a strong stimulus is used.

It must be emphasized that when widely separated electrodes and strong stimulation are used it is possible to pick up from the pial surface a small potential which is due to activation of tracts distal (or caudal) to the thalamic synapses. This is a common finding in the optic system whether a photic or an electrical stimulus is used (Marshall, Talbot and Ades, unpublished). Possibly a part of the primary response of Forbes and Morison (1939) represents the invasion of the cerebrum by the reaction. Under the conditions of our experiments the lemniscus contribution to the reaction picked up at the cortical lead is very small or negligible. In Fig. 7*c* for example, the very small response to the second stimulus may be due to the lemniscus action potentials, which at that stimulus interval would be nearly full sized (see following paper). Considerations such as these lead us to believe that our primary cortical response represents invasion of the cortex by the reaction.

The fact that tactile stimulation of a single small peripheral area gives rise in cats and monkeys to reactions at three primary cortical foci raises a point of interest. It was often observed that the amplitude of the reactions at the three regions varied independently during an experiment. This probably indicates that activation of any one is not necessary for the activation of any other and that each represents a specific thalamic projection. In the cat, regions 1 and 2 are within the somatic sensory area of Campbell (1905) while region 3 is not. Region 2 lies well within the foreleg sensory area as delimited by the strychnine method of Dusser de Barenne (1916) and region 3 is near the boundary of this area, but region 1 is always outside it. In general, the data we have secured in experiments on cats, though incomplete, agree with those recently presented by Adrian (1940). Adrian, however, apparently did not encounter region 1 for the forefoot and we have no information about the claw reactions which he has found. It must be conceded that the failure to record potentials from the "silent areas" surrounding the primary foci does not mean that these regions are not activated by that particular tactile stimulus; it only signifies that if such responses did occur they were below the threshold of the recording system. On the other hand, it is obvious that with the physiological stimuli used in our experiments, the consistent occurrence of maximal potential changes at the points indicated constitutes a significant clue to the organization of the primary projection system for cutaneous sensibility. To what extent this distribution as found under moderate and deep nembutal anesthesia, corresponds to that obtained in the unanesthetized animal has not been determined for the cat but in one animal, after emergence from ether anesthesia, the responses from region 2 were recorded by a fixed electrode. The primary surface positive responses were found to be essentially similar to those obtained under ether or nembutal.

In the monkey as in the cat primary cortical responses to weak tactile stimulation of a single peripheral point are found at three more or less discrete regions. The first of these appears to lie in Brodmann's area 3, the second is probably in area 1 and the third in area 2, possibly occasionally in area 5. Whether or not these reactions depend on conduction through separate thalamic pathways is an important question. The data obtained by Walker (1938) indicate that area 2 receives projections from the nucleus lateralis posterior but not from the nucleus ventralis posterior. The simplicity of the reactions suggests that only thalamic radiation fibers and local cortical "internuncials" participate in the elaboration of the primary responses. Though we have no direct evidence on the point, we feel it is reasonable to believe that the major foci are activated by separate thalamic projection bundles, and that their distribution merely reflects thalamic organization.

The size of the submaximal margin and the degree of overlap make it difficult to interpret the theory of a punctate representation of the periphery on the cortex in the light of our results. They lend no support to the view that a point *a* on the sensory cortex can be activated only from a cutaneous point *A*; on the contrary they show that *a* is almost certain to be within the sub-

maximal margin of the reactions set up by stimulation of a peripheral point in the neighborhood of *A*. Yet the fact that the general distribution of the responses set up by stimulation of a peripheral point shows a high degree of stability is in entire accord with the idea that the pattern of response is based on a stable and anatomically specific system of neurones.

The data secured in experiments on etherized and on unanesthetized monkeys answer certain questions concerning the nature of the primary response. It is clear that a large part of the difficulty in making observations on such preparations is due simply to the coincident and unrelated occurrence of spontaneous cortical activity or "brain waves." Since the evoked response is not *always* affected by a coincident spontaneous wave or one which occurs just previous to it, it follows that the spontaneous wave which is led from that electrode, does not always occupy, or modulate the activity of, the same neurones which participate in the evoked response. But attenuation or amplification of the evoked response by a preceding spontaneous wave occurred sufficiently often to indicate that the sensory neurones involved in the cortical reactions are also involved in the elaboration of, or are modulated by, some of the brain waves. Therefore we assign part of the variability of the primary response in the unanesthetized animal to a simple interference effect and part of it to physiological interaction between spontaneous activity and the primary response.

One of the important questions concerning the primary cortical sensory reaction obtained under nembutal is whether its consistency of occurrence and amplitude are altered by the anesthetic. This question is important because, with a quiet cortex resulting from deep anesthesia, the high amplitude and low threshold of the primary reaction suggest that the excitability of the sensory neurones responsible for it is not markedly decreased by the narcotic. If we assume, as suggested above, that some of these neurones participate in the spontaneous cortical activity of the unanesthetized animal the reduction of such activity under anesthesia, especially barbiturate anesthesia, would mean that they are relatively idle and always ready to discharge when activated by the afferent impulses set up by the peripheral stimulus. If this assumption is true, the prominence and regularity of the primary reactions under barbiturate anesthesia are essentially anesthetic artifacts, and the reactions would be smaller in the unanesthetized animal or in an animal under ether in which spontaneous activity is present to a marked degree. A comparison of the results obtained in unanesthetized animals with those secured in animals under ether, nembutal, dial or chloralosan gave an unequivocal answer to this question. Regardless of the presence or absence of anesthesia (any of the anesthetics used) primary surface positive reactions of the same order of magnitude were consistently evoked by weak tactile stimuli. When light nembutal anesthesia was deepened the responses were usually reduced somewhat, but never by more than about 20 per cent. Since the method of tactile stimulation was not sufficiently quantitative over long periods of time to permit us to claim that these measurements were com-

pletely decisive, we obtained further information by stimulating a peripheral nerve with supramaximal shocks first under conditions of light nembutal anesthesia and then under nembutal sufficiently deep to considerably reduce spontaneous activity. The results were in accord with those obtained with tactile stimuli, *i.e.*, the decrease in amplitude was at most not more than 20 per cent; usually it was much less. In all these experiments it was found that the latencies of the primary cortical responses were not significantly changed by any anesthetic. The records in the three columns of Fig. 6 illustrate this point.

Another question of importance is whether the degree of localization and the spatial distribution of the primary cortical reactions to tactile stimulation of a single peripheral point are the same in the unanesthetized monkey as in the animal under nembutal. While extensive exploration of the cortex was impossible with the groups of five electrodes used in the experiments on unanesthetized animals, the maximal (or nearly maximal) primary responses which we observed in the four monkeys studied after release of ether occurred at approximately the same cortical points as did those evoked by the same stimulation in other monkeys under nembutal anesthesia. Further, the limited exploration permitted by the five electrodes of a group showed that in the absence of anesthesia, just as with nembutal, areas giving little or no response lie very close to every spot of maximal response. As already pointed out, the extent of the submaximal margin is almost impossible to determine in the unanesthetized animal because of the difficulty of observing small evoked responses against the background of large spontaneous waves (Fig. 5*a*, *b*). Obviously the limited number of electrodes applied has not permitted detailed determinations of the spatial distribution of the primary cortical reactions to tactile stimulation of a single point. In spite of their deficiencies in certain aspects the results obtained in the absence of anesthesia indicate that the characteristics and the distribution of the cortical responses observed under nembutal have real physiological significance.

It is clear that in the somatic sensory system the primary cortical response is a distinct entity, and that the response to cutaneous stimulation does not consist merely of an alteration in frequency and amplitude of the spontaneous activity as claimed by Kornmüller (1937) and others. It is also clearly evident from our results as well as those obtained by Gerard, Marshall and Saul (1936) that the cat possesses a definite cortical representation of cutaneous sensibility, a fact which was questioned by Kornmüller because of his failure to observe that discrete responses are evoked by stimulation of the skin.

Although the primary response is little affected by anesthesia the reactions which follow it, and presumably result from it, are clearly influenced by anesthetics. The first type of secondary response was observed and investigated in only two experiments, which were done under light chlorolosan anesthesia; the second type was found only under deep nembutal anesthesia. The multiple response illustrated in Fig. 7 was occasionally observed in

response to tactile and electrical stimuli in animals under nembutal, but it was never as prominent as in the absence of anesthesia. Another significant effect of anesthesia is on the recovery cycle. In the observations on monkeys which were made after release of ether and then with nembutal anesthesia, electric shocks were applied to a toe or digit, a method which is inferior to that used in securing data from anesthetized animals (Fig. 8) for the reason that the successive shocks are probably not as regularly reproducible and also because there is no way of determining their strength in relation to the maximal for the cortical response. If under nembutal submaximal shocks are applied to the superficial radial nerve, a second response may be obtained at any interval after the first stimulus, but the size of the second response decreases as the intervals are made shorter. In some experiments on unanesthetized monkeys the response to the second shock, after passing through a minimum at an interval of approximately 20 msec., increased in size as the stimulus interval was further shortened. Hence, the failure to demonstrate an absolutely unresponsive period was not due to the use of submaximal stimuli, but rather to the fact that facilitation effects intervened to increase the excitability of neurones which were in the subliminal fringe of the first reaction. Thus the apparently shorter recovery times found in light ether and in the unanesthetized animals may have been due to a shorter recovery time of all or a fraction of the neurones concerned in each successive reaction. Also the facilitation effect may bring into action neurones which in nembutal anesthesia are always unresponsive to that stimulus. Probably both of these conditions operate to produce the effect under consideration.

Summary

1. The application of a brief tactile stimulus of low intensity to a very small cutaneous area evokes discrete surface positive potential waves in specific places on the contralateral cortex of the cat or monkey. These potentials constitute the primary cortical response to sensory stimulation.

2. In the cat a weak tactile stimulus applied to hairs on the dorsal surface of the forepaw (the only peripheral area given detailed examination) evokes separate maximal primary responses at three regions on the contralateral cortex. In the monkey the application of such a stimulus to any part of the body always evokes, within the cortical area of representation of that part, primary responses at two or more regions. The response having the shorter latency occurs in area 3 (Brodmann) the other with slightly greater latency is usually found in area 2. A third region of maximal primary response is often found in or very near area 1.

3. Each region or spot of maximal primary response is surrounded by a fringe or margin of submaximal responses. The overlap of the submaximal margins for peripheral regions which are adjacent or which have adjacent cortical representations is reciprocal and definite. Demonstrable interaction is usually found within the overlap.

4. Nembutal and certain other anesthetics greatly reduce the sponta-

neous activity of the cortex but do not appreciably affect any characteristics of the primary response except the recovery time, which is greatly prolonged.

5. Moderate ether anesthesia does not reduce the spontaneous activity of the cortex and it does not appreciably affect the threshold, latency or size of the primary response. With ether (even extremely deep ether) the recovery time is shorter than with nembutal. With light and moderate ether the absolutely unresponsive time is very short.

6. The primary response is present in the absence of anesthesia. As compared with the responses evocable in the anesthetized preparation those of the unanesthetized animal are characterized by a shorter recovery time of the primary response, greater complexity of various secondary reactions, and the occurrance of long lasting facilitation effects.

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OBSERVATIONS ON SUBCORTICAL SOMATIC SENSORY MECHANISMS OF CATS UNDER NEMBUTAL ANESTHESIA*

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INTRODUCTION

THESE EXPERIMENTS were undertaken to secure further information about the electrical responses in the central nervous system resulting from tactile stimulation in the anesthetized animal (Gerard, Marshall and Saul, 1933, 1936; Marshall, Woolsey and Bard, 1937, 1941; Bard, 1938). One aspect of the tactile reaction which appears to show less correspondence to the normal perception of sensation than any of the other characteristics is the length of the recovery time; under certain barbiturate anesthetics it appears to be of the order of 25 to 50 msec. Hence, particular emphasis was put on ascertaining the central level at which this effect occurs. Other information contributing to a physiological analysis has also been obtained.

Because of the difficulty of quantitating mechanical tactile stimulation of the peripheral end-organs, electrical shocks applied to the superficial radial nerve were used extensively in the study of the recovery cycle of the system. This type of experiment is quite similar to that of Derbyshire, Rempel, Forbes, and Lambert (1936), except that the pick-up electrodes were placed at two or more points along the sensory pathways in midbrain, thalamus, internal capsule or cortex, and the response to tactile stimulation was used to determine the foci of reactions. To what extent any reaction was modified by stimulation of other afferents than those from the skin is not known, though the superficial radial is regarded as primarily concerned with cutaneous sensibility. This nerve, however, is not the only nerve which carries impulses evoked by tactile stimulation of the dorsal aspect of the forefoot. After it is cut a small response can always be obtained in the central nervous system on stimulation of this area. It was assumed that the A group contains all the fibers involved in the tactile response. To what extent a single shock, activating a large number of fibers simultaneously, produces aberrent and unphysiological responses is not known. This question has been adequately discussed by Barron and Matthews (1938) and by Bishop and O'Leary (1938) and need not be reviewed here. It was considered that first locating the electrodes by physiological stimulation and then observing the response to electrical stimulation reduced that possibility of error, and the entire series of experiments was predicated on this assumption.

* Certain aspects of these observations were reported by Dr. Philip Bard (1938) and by the author (1938).

† Partial report of work done by the author in the Department of Physiology, Johns Hopkins University, School of Medicine, while a Fellow of the National Research Council, 1936–1938.

METHOD

The arrangement of apparatus was similar to that described in the papers on the cortical reactions. The electrical stimuli used in these experiments were applied with silver electrodes and consisted of brief pulses from pulse generators driven through a coreless induction coil. In all experiments stimuli were delivered in a definite repetitive sequence, and all time parameters were under instant control by adjustment of appropriate electrical devices. The entire cycle of events occupied two to four seconds when definite measurements of recovery time were made. This cyclic repetition of the reaction may possibly give somewhat different results than one would obtain with aperiodic or random application of the stimulus sequence.

The cortical potentials were recorded with a monopolar electrode as previously described (Marshall, Woolsey and Bard, 1937, 1940). The subcortical electrode system used in these experiments was quite similar, electrically. The active lead consisted of the tapering point of a small steel suture needle, the maximum diameter of which, with insulation, was 0.6 to 0.8 mm. After completely insulating the needle by application of many coats of enamel the tip was scraped off on a hand stone. The length of the tip used in different experiments varied from about 0.01 mm. to 0.5 mm. In principle, these steel needle electrodes are similar to those used by Renshaw, Forbes and Morison (1938, 1941), though they differ in both physical dimensions and polarizing characteristics.

The cats were anesthetized by intraperitoneal injections of nembutal, dial, or chlorolosan. Ether was used in two experiments. The larger veins and arteries supplying the temporal muscle were tied and the muscle removed. A large area of the cortex extending from the frontal pole to the tentorium was laid bare. This was done to provide an exposure sufficiently large for the insertion of needle electrodes and for the exploration of the surface with a thread electrode. Wide exposure also aided in reducing the tissue displacements due to arterial and venous pulses, which are quite small under barbiturate anesthesia but seriously large with ether.

The superficial radial nerve contralateral to the cranial opening was exposed and one of the smaller branches innervating D3, D4, or D5 or sometimes a larger branch innervating all three of those toes, was dissected free over a distance of two to four cm., after which the skin was lightly sutured to protect the nerve until the electrodes were applied. The nerve was not cut peripherally. It was used instead of the sciatic, because the primary cortical foci for the sciatic nerve responses are found medially on the cortex near the sagittal sinus, a region difficult to expose without interference with the cortical circulation (Adrian, 1940; Marshall, Woolsey, and Bard, 1941).

The cat's head was fixed in a Horsley-Clarke instrument carrying two electrode holders, each of which was used to place a subcortical needle electrode. The cortical electrode was fixed to an arm carried in a universal bearing, which was clamped to the frame of the Horsley-Clarke instrument in a position permitting exploration of the rostral part of the cortex.

In all of these experiments Horsley-Clarke coordinates were used not to determine the exact subcortical position at which to make observations, but merely to indicate the region to be explored. Exploration was systematically carried out to find the positions at which definite responses to physiological stimuli (mechanical displacements of hairs on the forefoot) were obtained. Three regions were investigated: the tegmental course of the lemnisci, the region of the ventrolateral nucleus of the thalamus, and the region in or near the internal capsule containing the thalamic radiations. Usually not more than two or three trials were required to place the electrode at an active point in any one of these regions. A definite response was considered to be present if the potential complex evoked by a weak tactile stimulation of the hairs on the dorsal surface of the forefoot was from 50 to 200 μV. When a maximal response was found along the needle track the needle was left in that position. After two electrodes had been thus located in the above mentioned regions, one of the branches of the contralateral superficial radial nerve was uncovered and placed on two pairs of silver electrodes. The distal pair was used to stimulate the nerve and the second pair to observe the action potential evoked. The shocks applied were usually supramaximal for the A fibers and sufficiently strong to produce a primary cortical response of maximal amplitude.

At the conclusion of several representative experiments the brains were prepared for histological examination. Before removing the head from the Horsley-Clarke instrument the remaining half of the calvarium was removed and the falx excised. A flat sharp knife

mounted on one of the electrode holders was manipulated to cut the brain partially into blocks approximately 10 mm. thick. The brain was then removed and put into 10 per cent formalin. A day or two later its division into blocks was completed and each block cut serially in sections 100 to 150μ thick by a frozen sectioning technic (Marshall, 1940, with improvements). Sections containing the electrode tracks were mounted on slides and stained by an iron haematoxylin method. Since the plane in which the sections were cut was determined by the cuts made by the knife mounted in the Horsley-Clarke needle holders, the electrode holes were approximately parallel to the plane of section and identification of position and depth was usually very easy. In practically all cases the needle was pushed through the region of maximum response and then withdrawn to that point. This procedure may introduce a slight error in determining the exact electrode position at which the observations were taken. The shrinkage of the tissue was so small, however, that measurements made from both ends of the needle track, when compared with the readings from the scale on the needle-holding device, were considered to be sufficiently accurate.

Results

More than 20 experiments were carried out, in which observations were made on the reactions in the tegmental regions, the thalamus, and internal capsule, and on the pial surface of the sensory cortex. The results will be discussed principally in terms of certain representative experiments which illustrate the more important features of the observations.

Tactile stimulation evokes in the tegmental region action potential complexes of two general classes. The first is characterized by a relatively short duration, a more obvious spike composition than the other, and a shorter relative recovery time, *i.e.*, shows relatively little attenuation as the stimulus interval is decreased to 5 or 10 msec. We believe this reaction to be, primarily, a fiber tract response due to conduction in what are conventionally considered to be second order neurones leading from the cord to the thalamic nuclei, *i.e.*, fibers of the spinal lemniscus. In most experiments this reaction was found in a restricted region just medial to the lateral lemniscus, dorsal to the substantia nigra and lateral to the caudal pole of the red nucleus (Fig. 1*g*). This locus typically gave a spike-filled base line (Fig. 1*d*) on which the evoked response was superimposed. Its position was often so near the lateral lemniscus that it was always necessary, as in the case of the response at cortical region 3 (Marshall, Woolsey and Bard, 1941), to determine if the response was auditory or somatic in origin.

The second class of response has been observed in many places throughout the midbrain. It consists of potential complexes which have smoother outlines, and, as a rule, are of a longer duration than those of the first class. They have longer relative recovery times, and undergo greater attenuation when the stimulus interval is decreased to 5 or 10 msec. For reasons which will be discussed later, after description of the more decisive thalamic reactions, it is believed that these reactions represent activity of second and third order neurones.*

The region in which the medial lemniscus can be clearly identified gives

* The terms second and third order are used in the conventional anatomical sense. Recent work of Toennies (1938) and Hursh (1940) indicates the need for caution in using these terms.

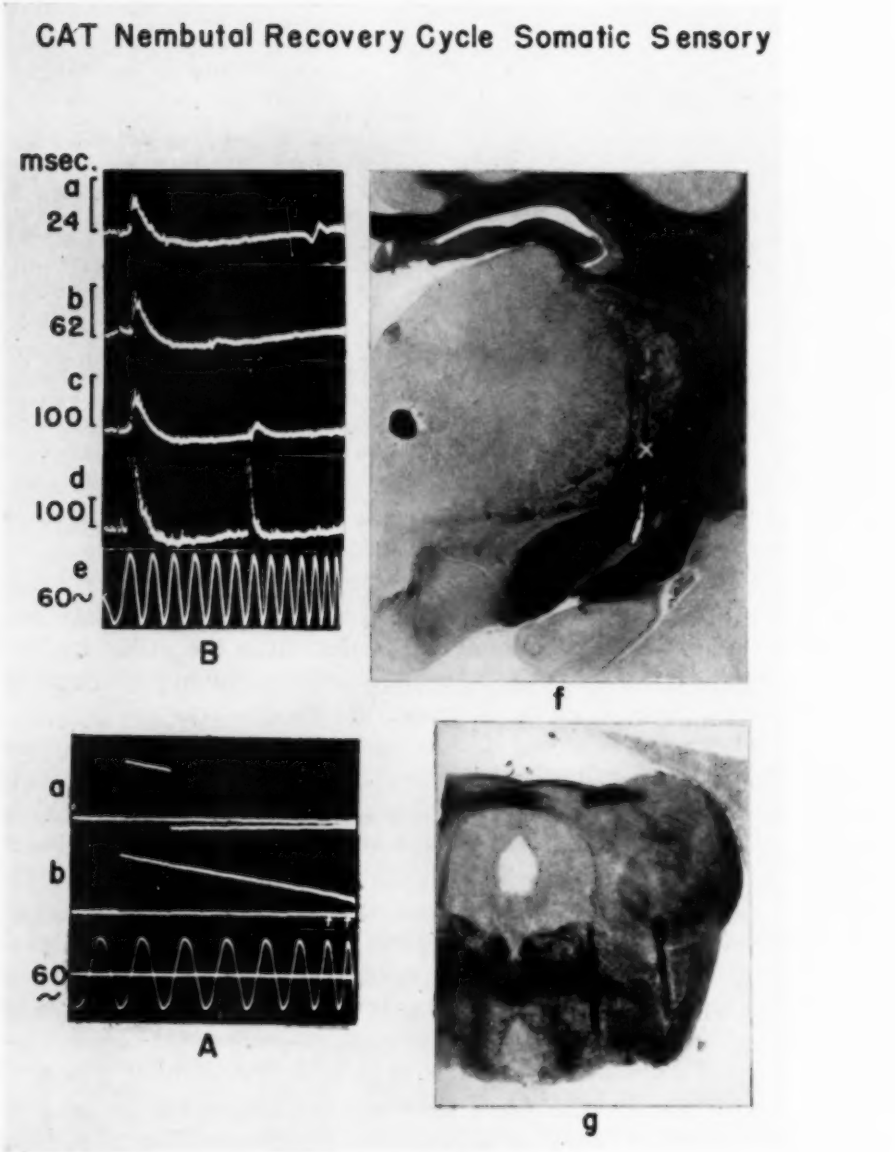

FIG. 1A. Showing essential characteristics of the recording system. (*a*) A rectangular calibrating pulse 18 msec. in duration and 100μ volts in amplitude. (*b*) Same voltage, but longer duration. First arrow indicates 93 msec. Time line = 60 cycles.

B. Cat, Nembutal, 3/21/38. Records from radiation fibers (*a*, *b*, *c*) and from spinal lemniscus fibers in tegmentum (*d*) with pictures of the sections showing approximate locations of the electrodes. Vertical line at left of record = 100μ volts. Stimuli were single electrical shocks applied to superficial radial at intervals indicated in msec. at left of records. Stimulus sequence—3 second cycles. Pick-up electrodes located by physiological stimulus.

(*f*) Middle needle track was the only one giving a significant response. Records *a*, *b*, and *c*, taken from center needle tract at point marked by *x*. (*g*) Ventral end of lateral needle

a response, the characteristics of which are intermediate between these two general classes. An example is shown in Fig. 2*n*.*

On the rostral side of the thalamic nuclei evoked and "spontaneous" activity are most clearly recorded from the internal capsule, where the electrode is relatively far from cell masses or synapses. In moderate and deep barbiturate anesthesia this region shows much less random spike activity than the tegmental region (Fig. 1B, *a*, *b*, *c*). Slow components ("brain wave activity") are present to a small degree. The occurrence and amplitude of these barrages parallel approximately the spontaneous activity on the cortex; both decrease as anesthesia becomes deeper. The evoked response obtained in this region (internal capsule) differs in several particulars from that seen in the lemniscus. The potential complex has a longer duration and exhibits longer relatively and absolutely unresponsive times† (Fig. 1B, *a*, *b*, *c*). The thalamic neurones which transmit excitation evoked by application of the first electrical shock to the superficial radial nerve are clearly not accessible to the reaction resulting from a second identical shock delivered 45 to 50 milliseconds later.

It is to be noted that the cortical reaction approximately parallels the reactions in the internal capsule in respect to the recovery times (Fig. 2 and 4). In no given case can one be certain that the electrode in the internal capsule is sampling a representative output of the thalamic nucleus, but the many experiments done yielded data of sufficient consistency to exclude that possibility of error. In all experiments in which the internal capsule electrode was more than a few millimeters from the ventrolateral nucleus pars externa, no electrical sign of any response was seen during the absolutely unresponsive period of the cortical response. If, however, the electrode was closer to the thalamic nucleus, a small diphasic spike (Fig. 1B, *a*, *b*, *c*) regularly appeared following an electrical stimulus applied within the cortical absolutely unresponsive time. As the electrode is moved still closer to the ventrolateral nucleus pars externa, the diphasic spike becomes larger and nearly mono-

* Later components in the lemniscus barrage due to stimulation of higher threshold and lower velocity groups in the superficial radial were seen but not observed with sufficient care to warrant their discussion here.

† "Unresponsive" is used instead of "refractory."

track is point at which response was evoked by physiological stimulation of contralateral forefoot. Physiological stimulus produced no significant response along the medial needle track (usually some response was obtained in this region). In all cases the electrical stimulus was maximal for the reaction in *a*, *b*, *c*, and *d*. Stimulus intervals indicated to left of potential records. *Note:* (i), the difference in intensity of tegmental and radiation responses for the second stimulus in *c* and *d*. (*ii*), small diphasic spike which appears essentially unchanged at very short intervals (*a*, *b*, and *c*). (iii) how slow wave in records *a*, *b*, and *c*, may be partly due to generalized spread effects from the ventrolateral nucleus. (iv) the higher level of random spike activity in the tegmental locus (*d*), even though amplification for record (*d*) was only half that of *a*, *b*, and *c*. (v) triphasic wave near end of trace in *a*. Shape indicates that electrode was some distance from site of this reaction. It is probably similar to the secondary response of Forbes *et al*. This wave, or one associated with it, also appeared on the cortical records of this experiment.

phasic. In this form it closely resembles the positive lemniscus spike found in the nucleus (see below). It is, therefore, possible that the spike obtained from a point in the radiations near the nucleus represents an "electrical spread" effect of the discharge of the lemniscus fibers or their endings or both. If this is true it appears to differ from usual cases of spread in that the spike retains fairly sharp features. The point was not determined with sufficient care, but the author has the impression that this spike was picked up only when the electrode was intercepting fibers of thalamo-cortical neurones which had just discharged to the cortex and, were, therefore, unresponsive, or refractory. If this is the case it is an example of transneuronal electrotonic conduction. In the cortical regions examined no response has been found within the absolutely unresponsive time which could be associated with the spike in the radiation. (It would be more accurate to say that if any such response was present it was below the threshold of the recording system.) The direct path from cord to cortex suggested by the experiments of Dusser de Barenne and McCulloch (1939) could provide a satisfactory explanation for this spike only if we assume that the cortical reaction associated with it was overlooked in our experiments.

The latencies of the reactions at the various levels show that the time for transmission from the tegmental region to the cortex is only 1 to 3 msec. With electrical stimulation of the superficial radial the lemniscus latency was 4 to 6 msec., that of the internal capsule 5 to 7 msec., and the cortical latency was usually about the same as that of the internal capsule. The tegmental latency is a little shorter than that observed by Leese and Einarson (1934) in the medulla for sciatic stimulation. With physiological (tactile) stimulation all latencies were greater.

A more coherent picture of the entire cycle of events is seen when an electrode is placed in the region of synaptic transfer in the ventrolateral nucleus pars externa (Fig. 2*e*, *f*, *g*, *h*, *i*, and *j*). Here the reaction has certain definite features. First, it shows a sharp wave made up of summated positive spikes which undergoes relatively little attenuation as the stimulus interval is decreased to 5 or 10 msec. This behavior obviously parallels that of the spinal lemniscus discussed above. It is believed that both represent lemniscus activity, and that the sharp wave in the thalamus represents the summed action potentials of the lemniscus fibers and of their terminal branches. This lemniscus component of the thalamic reaction is seen clearly only within the absolutely unresponsive period when the spikes associated with synapse transfer are absent (Fig. 2*h*).

Secondly, there is, following the lemniscus spike, a barrage of (apparently) diphasic and purely negative spikes which lasts approximately 10 to 15 msec. The duration of this barrage is of an order of magnitude comparable with that of the internal capsule barrage and the cortical wave. The ventrolateral nucleus pars externa was the only locus found in these experiments which regularly gave spikes having significant negative phases. For reasons which will be discussed in detail later, it is believed that this spike barrage

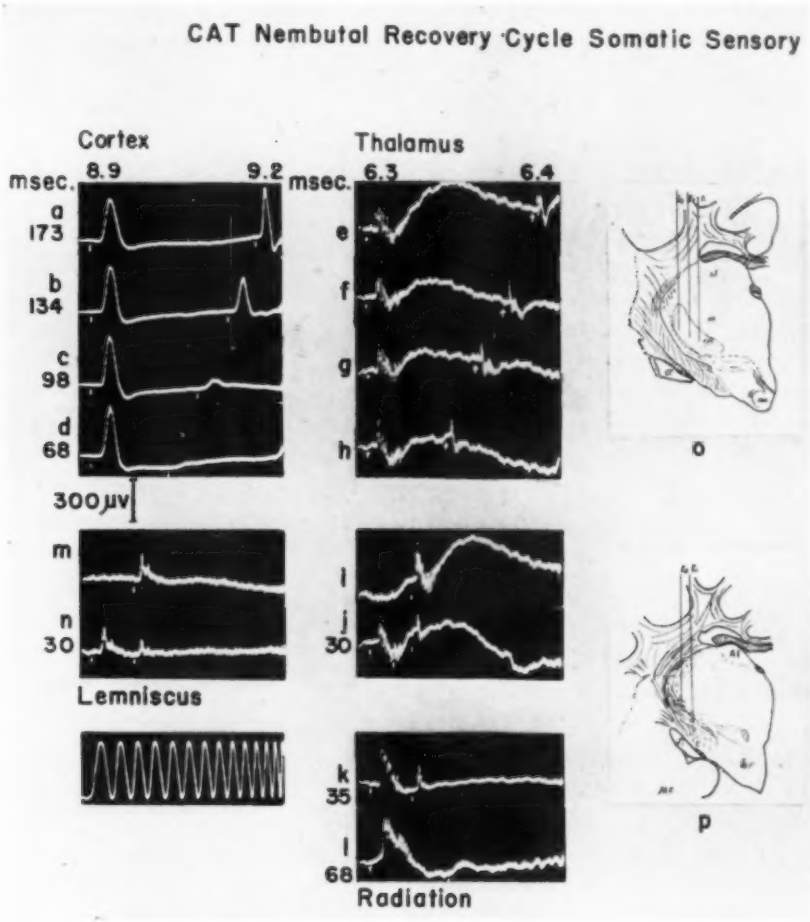

FIG. 2. Cat, Nembutal, 3/11/38. Electrical shocks to superficial radial at intervals indicated at left of each record, except for *e*, *f*, *g* and *h* which are same intervals as *a*, *b*, *c* and *d*, respectively. First shock slightly submaximal for the reaction. Interval in *a* is approximately total recovery time, atypically long in this experiment. *a*, *b*, *c*, and *d*, cortical records (region 3) at intervals indicated in msec. to left of each record. Records *e*, *f*, *g*, *h*, *i* and *j* from ventrolateral nucleus pars externa (E2, middle needle track in *o*). Record *i* is control on second stimulus. Irregular oscillations not typical and partly due to 60 cycles. Note that component designated as lemniscus detonating spike (or wave) is clearly distinguishable only when second stimulus falls in refractory period of the thalamic reactions (*h* and *j*). Record *k* from E1, medial needle track in *o*. E1 apparently picked up only lemniscus component. *m* and *n* lemniscus reaction from a medial position where medial lemniscus was located, and shows long relative recovery time (compare Fig. 1). Record *l* from radiations (E2 in *p*). Note length of barrage and absence of lemniscus detonating spike. Amplification for cortical records indicated below cortical column. All other records taken at 3 times that sensitivity.

represents essential signs of synaptic transfer. There is the added possibility that internuncial activity is contributing to the reaction. It is to be noted that, as the stimulus interval was decreased this spike barrage decreased in

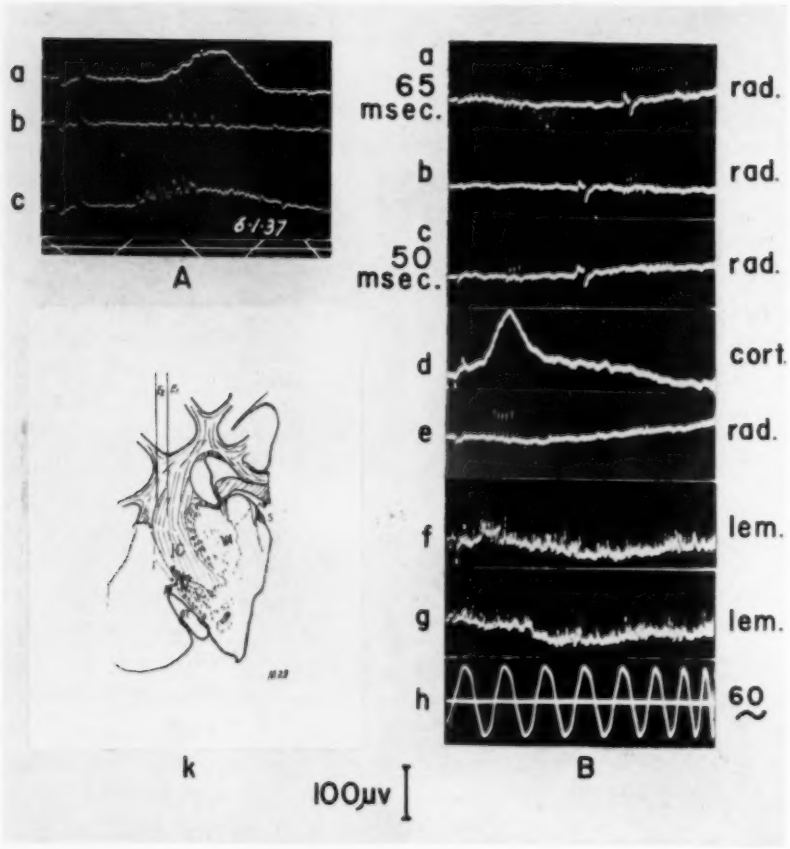

FIG. 3. Spike behavior of lemniscus and radiations following physiological stimulation of receptors about base of hairs on contralateral forefoot.

A. Cat, Nembutal, 6/1/37. *a*, cortex region 2; *b*, radiations in internal capsule; *c*, lemniscus in tegmentum.

B. Cat, Nembutal, 3/29/38. *a*, *b*, *c*, and *e*, spikes from electrode E2 in tracing *k* of section. *d*, cortical response region 3. *f*, response in lemniscus, approximate location of electrode same as lateral electrode in Fig. 1, *g*, or E5 in Fig. 4, *n*. *g*, control on lemniscus base line, no stimulus. Intervals between stimuli in *a* and *c* indicated at left of records. *b* is control on second stimulus. *Latencies:* (*a*) first stimulus to first spike 15.1 msec. Intervals between spikes in order 1.9–2.1–2.4 msec. Second stimulus to first spike 30 msec.; spike 1 to spike 2 interval 2.4 msec. (*b*) second stimulus only, latency to first spike 17.2 msec. Intervals between spikes in order, 1.8–1.8–2.4–3.0 msec. (*c*) first stimulus to first spike 16 msec. intervals between spikes in order, —1.6–1.7–2.2 msec. Latency second stimulus to spike—30 msec. (*e*) this group has a shorter latency than above groups, about 12 msec. and was probably a different axon since the electrode was moved a fraction of mm. after it was taken and before the above records were made. Note also that notches are on peaks of spike in *e*. (*f*) lemniscus barrage, latency 6.4 msec. All latencies except in *e* measured on 3 × enlargements of original records at a resolution of about 0.66 msec. per mm. Amplification indicated and same for all records.

duration; it has nearly disappeared in the example shown in Fig. 2*h*, at an interval of 68 msec.

A third feature of the response in the region of thalamic transfer is a long,

slow positive wave of significant amplitude. Its duration is comparable to that of the thalamic recovery time. There is apparently a definite interval between the lemniscus detonating spike and the initiation of this wave, and this interval is at least approximately occupied by the diphasic spike barrage (Fig. 2*e*, *f*, *g*, *h*, *i*, and *j*). The peak of the slow positive wave is at or near the end of the absolutely unresponsive period of the thalamic neurones as determined under the conditions of these experiments, and a second stimulus applied at this time typically produces only a lemniscus spike. There is no diphasic spike barrage and no appearance of another slow positive wave which, if present, would be superimposed on the positive wave which follows the first stimulus. Several considerations suggest that the slow positive wave may represent a postsynaptic after-potential originating in thalamic neurones. The wave is so much longer than the possible period of temporal dispersion indicated by the period of diphasic barrage, that the after-potential waves associated with the individual spikes in the barrage must be occurring practically simultaneously and so must sum by simple addition. Finally, the shape of the wave suggests that its initiation is actually delayed for a considerable interval after the beginning of synaptic transfer.

That the apparent refractoriness of the thalamic nucleus is not a case in which the summed reactions of many units merely drop below the threshold of the recording system, has been shown by many examples of single unit activity (Fig. 3). As emphasized by Renshaw, Forbes and Morison 1938, 1940), an electrode presenting a very small area of contact is best for observing such behavior. However, we have not usually been successful in recording from individual fibers without manipulating both the electrode and the stimulus. It appeared that single neurone potentials could be picked up only by fortuitously activating but one fiber in a group (see also Adrian and Moruzzi, 1939). The example shown in Fig. 3 is rather typical; the electrode was not in the region of the capsule having greatest density of fibers, but near the periphery of it, and a weak tactile stimulus was shifted about on the cat's foot until the prominent response was restricted to one axon.

In these experiments groups of spikes of the type shown in Fig. 3 were often seen. Each spike is typically notched at some point and, in the capsule and lemniscus, the spikes are always predominantly positive and usually nearly monophasic. The position of the notch on the spike usually varies, probably because of slight shifts of the tissue relative to the electrode. Shifts of notches within a group may be due to vascular pulsations. The illustration shows this effect as typically seen. No progressive decrease of spike amplitude has ever been observed. The records presented in Fig. 3 represent responses to single and paired mechanical stimuli applied to hairs on the dorsal aspect of the contralateral forefoot and repeated at intervals of two seconds. It is seen that each first stimulus is followed by a group of 4 or 5 single spikes so nearly identical that it is quite reasonable to consider them the signs of repetitive discharge in a single axon. Each successive group does not repro-

duce accurately; sometimes 5 spikes appear, sometimes 3 or 4. This is most likely due to slight irregularities in the peripheral stimulus. Not more than 5 spikes have ever been observed in a single group. The interval between the last spike and the preceding one is invariably greater than that between the first and second, and many observations show a definite progression which is repeated in every group, each succeeding spike occurring at a slightly greater interval. The interval typically increases from approximately 1.8 msec. between the first and second spikes to approximately 3 msec. between the fourth and fifth spikes. There is, of course, no definite certainty in ascribing any one of these spike groups to any particular axon system. It appears reasonable, however, to consider them the basic units which, by simple algebraic summation, elaborate most of the action potential complexes and waves discussed above.

These spike groups behave with significant precision as regards recovery periods. In the example of the determination of the recovery time shown in Fig. 3B, a very weak physiological stimulus was used; it is the only one presented in which an electrical stimulus was not used. At the interval just longer than the absolutely unresponsive time, one spike appeared at a prolonged latency after the second stimulus (Fig. 3B*c*). Not every stimulus cycle elicited a second response, but at a certain interval (in this case 50 msec.) one spike occurred approximately 3 out of 4 times. Fig. 3B*b* shows the average response to a second stimulus, note the shorter latency as well as the completeness of the group. Fig. 3B*a* shows the average response to a second stimulus applied after a slightly longer interval. The latencies are given in the legend for Fig. 3. The first and second stimuli were delivered by separate camel's hair brush units, the effect of the first being slightly less than that of the second stimulus, so that in Fig. 3B*a* and *c*, only four spikes are seen following the first stimulus. In these records one can see small spikes just emerging from the base line and grouped around the second response. They are, presumably, from fibers situated a little farther from the electrode tip than the fiber giving the prominent spikes.

Many observations on these presumably single-unit reactions tend to give strong support to the idea that under these conditions the thalamic synapses exhibit a long and definite recovery time or subnormal phase. The entire subnormal phase cannot, however, be allocated to the thalamic nucleus because the lemniscus barrage following the second stimulus at, say, 20 msec., is somewhat attenuated. Since both the amplitude and the duration of the lemniscus complex are attenuated, bombardment of the thalamic synapses is smaller and the opportunity for temporal summation is less. The situation was partly controlled by using a single stimulus adjusted to give at various intervals within the absolutely unresponsive time a lemniscus complex of about the same shape and amplitude as did the test stimulus. Such tests indicated that within the subnormal phase, the thalamic excitability is decreased much more than the excitability of the cord and medulla.

With appropriate location of the electrode and appropriate control of the

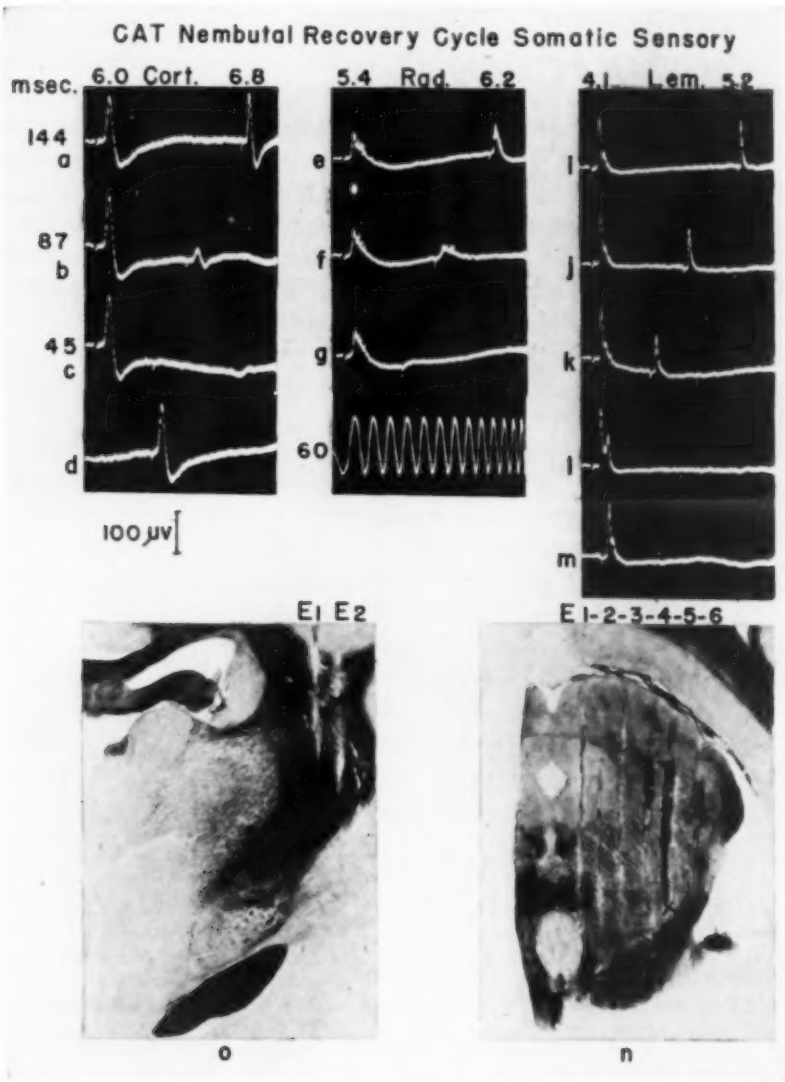

FIG. 4. Cat, Nembutal, 3/23/38. Electrical shocks to superficial radial; stimulus cycle of 4 sec. Records from cortex, radiations and tegmentum. Records *a*, *b*, *c*, and *d*, cortex region 3. *e*, *f*, and *g*, radiations from electrode E2 at point *x*, (*o*). *i*, *j*, *k*, *l*, and *m*, spinal lemniscus records from E5 at *x*, (*n*). Latencies for reactions in top records each column indicated above the reaction (msec). Latencies figured from 3 × enlargements, resolution approximately 1 mm. per msec. Intervals for *a*, *e*, and *i* indicated in msec. at left of *a*, etc. Amplification for cortical and radiation records indicated below cortical column, amplification for lemniscus records one half of that.

stimulus, single-unit spike potentials can always be recorded from the lemniscus. However, the constant high level of uncontrollable spike activity in the lemniscus confuses the picture (Fig. 3B*f* and *g*). At least a considerable portion of this activity can reasonably be ascribed to incidental and uncontrollable discharge from receptors throughout the periphery. As determined by

controlled stimulation the threshold of sensory receptors surrounding the hairs is so low that it is obvious that small displacements due to respiration, vascular pulsation, weak currents of air on the animal's surface, sound waves, as well as a probable low frequency discharge which cannot be assigned to any specific stimulus of the receptors (Fitzgerald, 1940) will discharge a steady stream of impulses to the cord and hence to the thalamus. This we shall refer to as *sensory tone*. In preparations under moderate to deep barbiturate anesthesia, there is a definite gradient of sensory tone across the thalamus; *i.e.*, the level of continuous spike activity in the internal capsule is always lower than in the lemniscus. This is presumably due to the subnormal phase effect, which permits transference of only a fraction of the impulses across the thalamic synapses. As anesthesia becomes lighter the level of spike activity in the internal capsule steadily rises and sums into waves which are similar to the spontaneous waves of the cortex, but the spike composition is either greater or more obvious in the internal capsule. The activity in the ventrolateral nucleus varies with depth of narcosis in a similar manner. This behavior is in agreement with the idea of the interdependence of the thalamus and cortex which has been repeatedly emphasized by Bishop and by Dusser de Barenne and McCulloch. Corticofugal discharges probably contribute to the wave-like barrages seen in the capsule under moderate and light anesthesia (Adrian and Moruzzi, 1939).

Another set of data is shown in Fig. 4. Here the lemniscus barrage was intercepted in the tegmentum, the thalamic output from the radiations relatively high in the internal capsule and the cortical response was recorded from region 3. Note the spikes discernible on the internal capsule wave.

Only brief mention of the injury discharges will be made. The barrage set up by a movement of the needle was often of high amplitude and usually for the first few seconds appeared to be diphasic. As the intensity (number of impulses per second) decreased it often became clear that the diphasicity was an illusion; individual spikes could then be seen to be either predominantly negative or positive and both types were intermingled. In the random distribution a negative spike had no apparent specific relation to a preceding or succeeding positive spike. From the data illustrated in Fig. 5, it is difficult to explain the positive injury spikes, but the negative spikes can obviously result from an impulse which is initiated near the electrode and propagated away from it. Different regions exhibit different patterns of injury potentials; for example, certain nuclear regions yield practically nothing but negative spikes. Both positive and negative injury spikes were commonly found in fiber tracts. Diphasic spikes were also seen and definite slow waves showing the characteristics of an injury discharge were rarely encountered except in the cornu ammonis where a decrementing rhythm was often observed. The injury potentials made observation of the evoked responses tedious because it was necessary to move the electrode downward in small discrete steps, pausing after each movement until the injury discharge had practically disappeared.

Discussion

The significance of the delimitations of these electrical reactions, the general description of the observations and the recovery times of the thalamic neurones, require some discussion.

First to be considered is the matter of locus of response. Some central regions, particularly when activated by physiological stimulation at the

periphery, exhibit such a very sharp localization of response that a displacement of the electrode of one or two tenths of a millimeter brings the tip into a silent region. This effect obviously is dependent on orientation of the active fiber tracts to the axis in which the needle moves, and on the dispersion of active fibers in the tract. The extreme limits of "electrical spread" effects can probably be safely estimated by consideration of the cases in which localization was sharpest, but it must be admitted that structural factors may cause a greater "electrical spread" in one direction than in another. The nearness of the electrode to active elements can also be estimated from

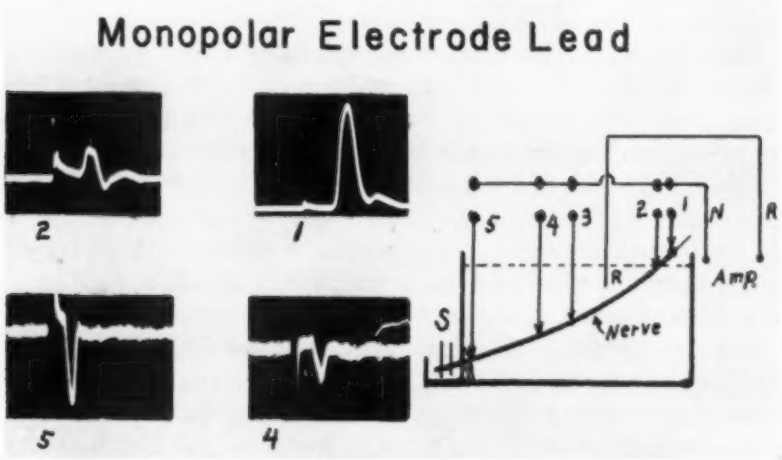

FIG. 5. Monopolar records of action potentials of a frog sciatic suspended in a Ringer's bath. S-stimulating electrodes, R-remote electrode (anywhere in bath more than a few mm. from nerve). Record 1 from electrode position 1, record 2 from electrode position 2, etc. Record 4 became positive when nerve was killed between 3 and 4. 8/10/37.

the amplitude and number of spikes composing the slow component. The point of maximal activity may thus be located, especially when a weak physiological stimulus is used, by evaluation of the amplitude and frequency of spikes and the amplitude of the slow wave. In the case of the more explosive reactions resulting from electrical stimulation at the periphery greater caution is necessary.

The sign of the reactions recorded from the midbrain, thalamus and internal capsule presents another question. The behavior of a "brain model" (Fig. 5) indicated that monophasic positive waves and spikes should be expected when recording from the killed end of a nerve along which impulses are being conducted toward the electrode, *i.e.*, that point never becomes a sink. However, if the impulse is conducted several millimeters beyond the electrode the negative phases remain relatively small. In most cases where the needle was in a fiber tract negative spikes were not prominent. In the case of the ventrolateral nucleus it is obvious that all or most of the ascending impulses in the lemniscus endings must be relayed through synapses. The

finding of negative spikes *here* does not, however, contradict the assumption that in the fiber tracts the potentials are recorded only from killed ends. In the latter case the propagation is, more or less, a straight line affair while in the thalamic synapse situation a cell on the "rostral" or "cortical" side of the electrode may be fired by a lemniscus or internuncial ending which lies lateral to the electrode.

In the synaptic regions the synapse time might be a factor operating to separate positive phases due to presynaptic activity from negative phases due to postsynaptic activity. Lorente de Nó's data (1938) indicate that the synapse time should be nearly equal to the duration of the action spike. One may therefore expect a more or less discrete temporal separation of the presynaptic and postsynaptic spikes if the electrode is in a position to record both (O'Leary and Bishop, 1939; Marshall and Talbot, 1940). The temporal dispersion unavoidably caused partly by conduction from the periphery but chiefly by activity of internuncials in the cord, makes it impossible to identify synaptic transfer entirely on the basis of negative spikes or negative slow components. It is thought that where they are discernible, the negative spikes are significant indications of synaptic transfer, and that their absence probably signifies that no significant synaptic transfer is occurring.

The thalamic reaction can be fitted into an interesting picture if the assumption is correct that the slow positive wave is a postsynaptic after-potential. Thus we would have the lemniscus detonating spike of short recovery time followed by a diphasic and negative barrage having a long recovery time which approximately corresponds to the length of the postsynaptic positive after-potential. Of particular interest is the pause between the lemniscus detonating spike and the beginning of the positive wave. It is probably more than an incidental fact that this interval is occupied by essential signs of synaptic transfer, and that its duration is about the same as that of the radiation barrage and the cortical wave. It would appear that the synapses are "open" until the positive wave rises from the base line and that they are closed until the positive wave reaches maximum after which the synaptic transfer roughly parallels, in an inverse manner, the descent of the positive wave to the base line. It is obvious that the evidence for such a relation between this after-potential and the recovery time is purely circumstantial. The magnitude of the positive wave is often very striking though the example shown (Fig. 2) was the highest seen in five experiments. However, if this is a positive after-potential in which the *entire* radiation neurone participates it is difficult to see why it is not recorded from the internal capsule, particularly if, as is probable, the internal capsule spikes are led from killed ends of fibers.

The entire thalamic potential sequence shows striking similarities to the records of spinal cord and root potentials presented by Hughes and Gasser (1934), Eccles and Pritchard (1937), Gasser (1939), Woolsey and Larrabee (1940), and Hughes, McCouch, and Stewart (1940). The chief differences between the thalamic and cord experiments appear to be that in the former

the leads were more directly applied and record the activity of a simpler mechanism; interpretation is, therefore, simpler in the case of the thalamic reactions. In these experiments a definite negative wave preceding the positive wave was sometimes seen. It cannot, however, be weighted very seriously because there is no indication as to what part of it may be negative after-potential and what part is due to simple fusion of the negative spikes which outnumber the positive spikes in the latter part of the synaptic transfer interval.

If the single-unit barrages in the internal capsule represent, as they probably do, repetitive discharges of single thalamic neurones, significant effects due to summation of subnormality should directly result from the frequency of the discharges (Gasser, 1935; Graham and Lorente de Nó, 1938; Lorente de Nó and Graham, 1938). The spikes composing these brief bursts occur at frequencies equivalent to rates of 500 to 300 per second, among the highest ever recorded in the nervous system. It should be emphasized that these high frequencies were obtained with very weak tactile stimuli. The complexity of the barrages prevented measurement of frequency when strong tactile or electrical stimuli were used.

The behavior of single unit barrages in the internal capsule also suggests that one function of the subnormal phase is to organize synaptic transmission into physiological quanta, a factor which serves to prevent excessive fatigue of the various parts of the central system and to prevent any one stimulus from gaining complete control of the final common pools. Before speculation can be carried further along this line a more adequate control of the period of central activation by the stimulus and observation under other anesthetics will be necessary. It is probable that the subnormal phase encountered under the conditions of these experiments is comparable to the silent period of reflex physiology, though all of the time relations are lengthened under moderate and deep barbiturate anesthesia. In the conscious animal comparable demonstrations of a definite recovery time for the cortical reaction cannot usually be made. Whether this is due to a vanishingly short recovery time, involving the given group of neurones, or whether the effect is merely masked by the greater complexity of the response plus greater excitability and alternation of the subliminal fringe is an important question concerning which we have no conclusive information (Marshall, Woolsey and Bard, 1941).

Most of the available data on silent periods observed elsewhere in the nervous system indicate that with continuous stimulation the silent period is followed by a discontinuous response at a lower frequency (equilibration). This phenomenon was also demonstrated in these experiments. If the weak physiological stimulus was repeated at a frequency of 15 to 20 per second each stimulus was followed on the average, by only one or two spikes. At higher frequencies alternation occurred. It is to be noted that spinal mechanisms are also involved in organizing and quantitating the stimulus delivered to the thalamic nucleus (Toennies, 1938; Hursh, 1940), hence these

experiments give no conclusive information concerning the response of the thalamic nucleus to the weakest activating stimulus, since the cord may amplify the stimulus from the periphery in an exponential manner, as well as lengthening the barrage. A weaker stimulus, however, does produce thalamic axon barrages of fewer spikes than a stronger stimulus (Fig. 3). Because of the buffering effect of the segmental system the data obtained give no conclusive information concerning the recovery cycle for strong stimuli which might be applied, electrically, to the lemniscus tract or directly to the thalamic nucleus.

The recovery time of the cortical reactions considered here (that of the primary projection foci) should not be confused with the recovery times of the secondary responses described by Forbes and Morison (1939) or those of the pyramidal discharges reported by Adrian and Moruzzi (1939). Forbes and Morison report that their primary response is subject to a fatigue effect. As mentioned above this was not seen in these experiments. Probably the essential factor preventing observation of such an effect was the cyclic repetition of the stimulus sequence, which kept the system equilibrated at a level at which the effect was negligible.

The work of Beecher, McDonough and Forbes (1938) suggests that depression of systemic blood pressure and respiration may be the chief factor responsible for the prolongation of the recovery time. Depression of blood pressure or failure of external respiration, does prolong the recovery time, decrease after discharge, spontaneous activity and summation or facilitation, but they do not appear to be the only factors. Experiments to control this point have been done in which systemic blood pressure was measured from the femoral artery. When observations were begun small quantities of nembutal were added either intraperitoneally or intravenously until the spontaneous activity was reduced to a low level. The blood pressure was usually reduced to 70–100 mm. of Hg and the recovery times varied from 30 to 50 msec. If the systemic blood pressure was now increased to 150–200 mm. Hg by administration of a small quantity of ephedrine HCl the recovery times were shortened to 25–40 msec., but other features of the reaction were not changed. It is to be noted that the rate of blood flow through the thalamus is the essential item in this situation and that has not been measured. Forced ventilation produced manually or administration of CO_2 did not change the time scale or intensity of the reactions. The fact that the effects characteristic of nembutal narcosis are encountered under ether only when anesthesia is dangerously deep, suggests that nembutal may act by decreasing cell respiration.

The prolongation of the refractory states of any one group of units involved in the elaboration of "brain waves" would obviously tend to abolish the rhythms. This may be the essential factor involved in the reduction (in incidence) of spontaneous activity by certain anesthetics, particularly nembutal, which in moderate depth leaves some systems, certainly the primary projection system, highly sensitive to discontinuous peripheral

stimulation, but greatly reduces the amount of spontaneous activity found within this system. On the other hand, we may assume that the anesthetic directly blocks certain internuncial activity necessary for the maintenance of spontaneous activity. "Internuncial activity" undoubtedly operates, in some manner, to modulate such basic reactions as the primary sensory responses. Hence, we might conclude that the considerable decrease in spontaneous activity usually occurring in these experiments, removed necessary facilitating factors, and by that means, prolonged the recovery time.

Having established a generalized electrical picture of the behavior of certain nuclear regions and the fact that the recovery time is a function of the anesthetic, these experiments also suggest that the information will be of value in determining the presence of synaptic transfer in cases in which the anatomical pathway is known with less certainty. It is obvious that the simplification of the primary sensory reactions and definite refractory behavior of the C.N.S. neurones, which is produced by barbiturates, may be a useful tool in the solution of certain other problems, since only the neurones not occupied by one reaction will be available for participation in a second reaction following in the refractory period of the first reaction.

In conclusion, the author must emphasize that the regions studied in these experiments are not the only ones in the brain stem in which definite reactions were evoked by stimulation of the forefoot region. It is believed, however, that the regions discussed are the most important in terms of intensity of reactions.

Summary

1. Under nembutal anesthesia a tactile stimulus applied to hairs on the forefoot of the cat consistently evokes measurable electrical reactions in the tegmentum, the thalamus, the internal capsule, and the cortex.

2. The reactions in the tegmentum and internal capsule, which are evoked by tactile or electrical stimulation of the periphery, appear as spike barrages 5 to 15 msec. in duration. The capsule barrage is either longer or it decrements more slowly than the lemniscus barrage and has about the same duration as the cortical wave.

3. In deep anesthesia the absolutely unresponsive time for the reaction rostral to the ventrolateral nucleus pars externa of the thalamus was found to be 25 to 50 milliseconds. The absolutely unresponsive time caudal to the thalamus was too brief to determine by the procedure used in these experiments. It appears that the mechanism chiefly responsible for the long recovery time is in the ventrolateral nucleus pars externa.

4. Three types of electrical activity resulting from the peripheral stimulus can be recorded from the thalamus. These are in order of occurrence (a) the lemniscus spike barrage which presumably detonates the thalamic neurones, (b) a burst of diphasic spikes of axon spike dimensions which is associated with activation of the radiations and (c) a long slow positive wave, the time course of which approximately parallels the recovery time and which probably represents a postsynaptic after-potential.

5. In the regions rostral to the ventrolateral nucleus pars externa, a definite absolutely unresponsive time is seen in the responses of single units as well as in the summed activity of many units.

6. It appears that a single thalamic neurone can discharge repetitively at a high frequency for 6 to 8 msec. (4 or 5 spikes in that interval) and that this repetitive discharge is due to a sustained lemniscus bombardment during that interval or longer. This brief, high frequency train of spikes represents a unit or quantum of activity after which the mechanism is refractory or unresponsive for a definite period as a result of summation of subnormality in each thalamic neurone involved.

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PUPILLODILATOR REACTIONS TO SCIATIC AND DIENCEPHALIC STIMULATION

A COMPARATIVE STUDY IN CAT AND MONKEY

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THE MECHANISM of reflex pupillary dilatation has long been a disputed point. Budge and Waller (1852) and Schiff (1875), using rabbits as experimental animals, considered that the dilatation was effected by excitation of the cervical sympathetic trunk (*C.S.T.*). Vulpian (1878) was able to show after removal of the stellate and superior cervical ganglion in the cat, that sciatic nerve stimulation still caused mydriasis. Braunstein (1894) could elicit no pupillary dilatation after section of the third nerve in cats, a finding contested by Anderson (1904). Recently, McSwiney and Suffolk (1938) and Ury and Gellhorn (1939), have demonstrated that the mydriasis obtained by stimulation of an afferent visceral or somatic nerve in cats is due to inhibition of impulses originating in the oculomotor nerve nucleus.

Pupillodilatation may also be evoked by stimulation of the hypothalamus and cerebral cortex. Karplus and Kreidl (1912) believed that impulses for pupillodilatation and retraction of the nictitating membrane (*n.m.*) obtained by hypothalamic stimulation in the cat, passed down the brain stem to the cervical cord and reached the eye via the cervical sympathetic nerve. Carlson, Darrow and Gellhorn (1940) found that stimulation of the hypothalamus in cats continued to dilate the pupil after section of the homolateral *C.S.T.* Pupillary dilatation has been obtained from cortical stimulation in both cats and monkeys. In cats Parsons (1901) found that good dilatation could still be obtained following section of the *C.S.T.* while in monkeys, Sherrington demonstrated that cortical stimulation no longer caused pupillary dilatation after interruption of the *C.S.T.* (See Sherrington 1940, p. 252).

Most of the experiments just cited were performed on cats or rabbits. There is comparatively little work on the pupillodilatation mechanism of primates. Since the cat and monkey differ markedly in the response of the denervated iris to adrenaline and acetylcholine (Bender and Weinstein, 1940), and to insulin hypoglycemia (Bender and Siegal, 1940), we have extended our study of the sympathetic and parasympathetic hormonal systems to the neural pathways for pupillary dilatation, and have compared the effects of afferent nerve with diencephalic stimulation in cats and monkeys.

MATERIAL AND METHODS

For these studies 35 cats and 18 monkeys (*Macaca mulatta*) were used. Save for terminal experiments all operative procedures were carried out with sterile precautions.

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Amytal, nembutal, urethane or light ether anesthesia was employed. The cervical sympathetic trunk was cut preganglionically in the neck, while the oculomotor nerve was sectioned intracranially. In monkeys a bone flap was made, the dura opened and the third nerve visualized by elevating the temporal lobe. In cats, the oculomotor nerve was approached through a trephine opening with removal of a portion of the temporal lobe. In several animals the third nerve nucleus was destroyed by the Horsley-Clarke technique.

Stimulation of the sciatic nerve was performed with a bipolar shielded electrode. The hypothalamus was stimulated with a bipolar nichrome electrode using the Horsley-Clarke stereotaxic instrument according to the procedure described by Ranson (1934). The stimulating current was drawn from a Thyrotron or Wyss stimulator.

Results

Sciatic stimulation—Cat.—Electric stimulation of the sciatic nerve produced pupillary dilatation, which was present after section of either the *C.S.T.*, the trigeminal nerve or both. The *C.S.T.* was interrupted acutely and preganglionically in order to eliminate the factor of adrenaline sensitivity in the denervated iris and *n.m.* The pupillodilatation obtained on the side of sympathetic section was prompt, and averaged 1 mm. less than the mydriasis observed in the normal eye. It was not accompanied by retraction of the *n.m.* or widening of the palpebral fissure, suggesting that the response was not mediated through the cervical sympathetic.* The mydriasis elicited by sciatic stimulation was abolished, however, by intracranial section of the oculomotor nerve even though the cervical sympathetic innervation was left intact. Dest uction of the caudal hypothalamus did not interfere with the sciatic pupillodilatation.

These findings confirm those of McSwiney and Suffolk (1938) and Ury and Gellhorn (1939), and they indicate that in cats the mydriasis resulting from sciatic stimulation may not be due to excitation of the sympathetic system, but to parasympathetic inhibition.

Monkey.—In the monkey, electrical or mechanical stimulation of the sciatic nerve produced a mydriasis in the normal iris. On acute section of the *C.S.T.* the reflex mydriasis was usually eliminated although in several macaques a slight dilatation could still be detected. The reflex pupillary dilatation obtained on electric stimulation of the sciatic nerve was not abolished by section of the oculomotor nerve where a definite dilatation may still be observed in the monkey's decentralized iris. This was consistently demonstrated and was in direct contrast to the findings after sympathetic denervation in the same animal. These observations suggest that reflex pupillodilatation in the monkey is mediated chiefly by the *C.S.T.* and not by parasympathetic inhibition which seems to be predominant in the cat.

Diencephalic stimulation—Cat.—Bilateral dilatation of the pupils was observed on stimulation of numerous areas in the diencephalon. In the thalamus and more dorsal regions of the hypothalamus the dilatation was usually unaccompanied by retraction of the *n.m.* This mydriasis was unaffected or only slightly diminished by section of the *C.S.T.* It was abolished

* Stimulation of the cervical sympathetic trunk produces dilatation of the pupil, retraction of the nictitating membrane and widening of the palpebral fissure.

by interruption of the third nerve fibers, indicating that the pupillary response is mediated chiefly by parasympathetic inhibition. Certain points were found in the ventral hypothalamus which yielded maximal pupillary dilatation accompanied by retraction of each *n.m.* This mydriasis could be considerably reduced but not abolished by section of the *C.S.T.* When such points were stimulated after severing the third nerve additional dilatation could still be observed in the decentralized iris, suggesting that here there was a preponderance of sympathetic activity.

Monkey.—Stimulation of the hypothalamus in the monkey also produced bilateral pupillodilatation. The dilatation from all points was greatly diminished or abolished by section of the *C.S.T.* Section of the third cranial nerve however did not abolish the mydriasis obtained on stimulating numerous diencephalic points. These observations indicate that the pupillary dilatation which results from electric stimulation of the hypothalamus of the monkey is mainly effected through excitation of the sympathetic rather than by inhibition of the parasympathetic supply as noted in the cat.

Discussion

It is apparent that the pupillodilator mechanisms in response to stimulation at various levels of the nervous system differ in the cat and monkey. Whereas in the cat, the resultant pupillodilatation is accomplished predominately through inhibition of the third nerve nucleus, in the monkey, the cervical sympathetic pathway plays a much more important role. Section of the cervical sympathetic trunk of the cat failed materially to alter the pupillary dilatation obtainable on stimulation of (i) afferent visceral and somatic nerves, or (ii) many diencephalic pupillodilator areas. In the monkey, however, excitation at any of these levels after interruption of the *C.S.T.* failed appreciably to dilate the pupil. After eliminating the parasympathetic mechanism by section of the third nerve, hypothalamic and sciatic stimulations furnished a better pupillary dilatation in the monkey than in the cat. Similar observations have been made by us in experiments involving stimulation of the cerebral cortex. In the cat good pupillary dilatation persists after section of the *C.S.T.*, while in the macaque stimulation of a point dorsal to area 8 of Brodmann no longer produces mydriasis on the side of the cut *C.S.T.*

It should be stressed though, that the excitatory sympathetic and inhibitory parasympathetic mechanisms are reciprocally related, and in both species each participates in the response of the iris to stimuli mediated by autonomic system. It might be inferred that because of its higher position in the phylogenetic scale, the balance of reciprocal innervation in the monkey is more finely developed. This however would not explain the apparent predominance of the excitatory over the inhibitory factor. The species difference is particularly significant when the findings are applied to man. It is stated that the cilio-spinal reflex, the dilatation of the pupil elicited by painful pinching of the skin of the neck, is abolished in Horner's syndrome. This

finding is in accord with the reflex pupillodilator mechanism found in primates, as opposed to the cat where interruption of the *C.S.T.* does not abolish the pupillodilator response to painful stimulation.

The elicitation of pupillary dilatation by stimulation of widely separated divisions of the nervous system provides another illustration of the Jacksonian concept of successive levels of autonomic function (See Fulton, 1939). At the lowest level, pupillodilatation is obtained by stimulation of an afferent nerve, constituting in the cat a relatively simple reflex arc in which impulses travel up the spinal cord and brain stem to the oculomotor nucleus, where inhibition takes place. The hypothalamus is apparently not an integral part of this basic pathway since large lesions of the posterior hypothalamus or thalamus in the cat, did not, in our experiments, abolish the reflex pupillodilatation obtained on sciatic stimulation. Karplus and Kreidl (1918) had previously found that the response did not persist after destruction of the hypothalamus, while Keller (1932) was able to obtain pupillodilatation in cats after brain stem transection at the level of the mamillary bodies from pinching the skin. The hypothalamus, therefore may be regarded as representing a higher, more complex level of autonomic function, serving to integrate pupillodilatation with other manifestations of sympathetic activity. At the cortical level pupillary action probably is regulated and even inhibited along with other autonomic modalities.

Points in the cat's diencephalon producing pupillary dilatation on stimulation have been mapped by Ranson and Magoun (1933). It is interesting that in our experiments a different mode of pupillary dilatation could be elicited from different areas of the diencephalon. In the thalamus and dorsal regions of the hypothalamus the mydriasis is accomplished chiefly by parasympathetic inhibition, for the response to stimulation is unaccompanied by retraction of the *n.m.*, is little affected by section of the *C.S.T.* and is abolished by cutting the oculomotor nerve. Sympathetic activity is more pronounced at points in the ventral diencephalon where maximal pupillary dilatation is accompanied by retraction of the *n.m.* This mydriasis is considerable diminished after section of the *C.S.T.* but is not abolished by severing the oculomotor nerve.

The pupillary dilatation obtainable on hypothalamic stimulation is probably a complex reaction in which the neural mechanisms, excitatory and inhibitory, are not the sole factors. It has been demonstrated (Houssay and Molinelli, 1925) (Magoun, Ranson and Hetherington, 1939) that hypothalamic stimulation may initiate a discharge of adrenalin by means of impulses travelling down the brain stem and over the splanchnic nerves. In a preliminary study we found that hypothalamic stimulation causes dilatation of the denervated iris in the cat, but not in the monkey. This is presumably due to adrenalin because bilateral adrenalectomy abolishes this mydriasis. We have shown previously (Bender and Weinstein, 1940), that the sensitized denervated iris of the cat has a predominately adrenergic (dilator) response while the monkey reacts with a cholinergic (constrictor)

effect to the introduction of either acetylcholine or adrenalin. It is of interest and not too surprising that there should be a species difference in the neural as well as the humoral aspect of pupillary dilatation.

Summary

1. Comparative studies of pupillodilatation obtained on sciatic nerve and diencephalic stimulation were made in the cat and monkey.

2. The reflex pupillodilatation obtained with sciatic stimulation in the cat was not abolished by section of the cervical sympathetic trunk, the trigeminus or by lesions of the hypothalamus, but the reaction was eliminated by section of the oculomotor nerve.

3. In contrast, this reflex pupillary dilatation in the monkey was abolished or greatly reduced by cutting of the cervical sympathetic, but it failed to disappear after section of the third cranial nerve.

4. Similarly the pupillary dilatation obtained by stimulation in the thalamus and dorsal hypothalamus in the cat was little reduced by section of the cervical sympathetic, and it could not be obtained after sectioning the third cranial nerve.

5. Stimulation of the hypothalamus in the monkey resulted in bilateral pupillary dilatation which was abolished, or greatly diminished, by section of the cervical sympathetic, but it was not abolished by destruction of the oculomotor nerve.

6. In each species pupillary dilatation is accomplished by both parasympathetic inhibitory and sympathetic excitatory mechanisms. In the cat, inhibition of the parasympathetic mechanism is predominant while in the monkey excitation of the sympathetic mechanism is of greater importance.

Experiment 1.—Sciatic and hypothalamic stimulations before and after section of left 3rd nerve, right and left C.S.T. [Hypothalamus M. 49].

April 10, 1940.—A grey, tan and white cat weighing 2500 grams was the subject of the experiment. The pupils were equal and reacted well to light.

11:10 A.M. 1.2 c.c. of nembutal given intravenously. The animal was placed in the Horsley-Clarke apparatus.

11:28.—Bipolar electrode placed at A11 R2 H-4. Both pupils measured 3 mm. in diameter.

11:35.—Hypothalamic stimulation for 5 seconds. Thyrotron stimulator frequency 40 per. sec. 5 volts. Both pupils dilated to 6 mm. No retraction of either *n.m.*

11:42.—Hypothalamic stimulation at A11 R2 H-6 gave dilatation of pupils to 8.0 mm. accompanied by retraction of both *n.m.* (a "sympathetic point").

11:46.—Left sciatic nerve exposed.

11:58.—Stimulation of sciatic nerve dilated both pupils to 6.0 mm. No retraction of either *n.m.*

12:00.—Intracranial exposure of left third nerve.

12:47.—Left third nerve transected.

12:48.—Left pupil is 9 mm. Right is 2.0 mm.

12:48.—Sciatic stimulation dilated right pupil to 5.2 mm. Left pupil did not dilate.

12:50.—Right pupil 2 mm. Left 8 mm.

12:57.—Stimulation at A11 R2 H-4 dilated right pupil to 5 mm. No dilatation of left pupil. No change in either *n.m.*

12:59.—Stimulation at A11 R2 H-6 dilated right pupil from 2.0 to 8.0 mm. and left pupil from 9 to 10.5 mm. Both *n.m.* retracted.

1:30.—Right *C.S.T.* exposed.

1:32.—Right *C.S.T.* sectioned preganglionically.

1:33.—Right pupil 1.0 mm. Left 8.5 mm.

1:52.—Stimulation at A11 R2 H-4 dilated right pupil from 1.0 to 4.0 mm. No change in left pupil, no change in either *n.m.*

1:56.—Stimulation at A11 R2 H-6 dilated right pupil to 4.0 mm. and left pupil from 8.5 to 10 mm. Left *n.m.* retracted. No change in right *n.m.*

2:00.—Sciatic stimulation continues to dilate the right pupil to 4 mm. but has no effect on the decentralized left iris.

2:30.—Right pupil a slit. Left is 8.5 mm.

2:35.—Left *C.S.T.* exposed and sectioned. Stimulation of iris end gives dilatation of pupil to 12 mm. retraction of left *n.m.* and widening of the palpebral fissure.

2:40.—Right pupil 1.5 mm. Left pupil 8.5 mm.

2:50.—Stimulation of hypothalamus at A11 R2 H-6 now produced no dilatation of left pupil or retraction of either *n.m.* The right pupil dilates to 4 mm. Cat sacrificed.

Brain section showed a needle track in the tuber region, 1.5 mm. to the right of the midline. The point A11 R2 H-4 was in the dorsal hypothalamus in the region of the principal filiform nucleus. The point A11 R2 H-6 was at the border of the ventromedial hypothalamic nucleus.

Experiment 2.—Sciatic and hypothalamic stimulations after lesions of right 3rd nerve nucleus, before and after crushing of right C.S.T. and section of left oculomotor nerve [Hypothalamus M. 38].

May 22, 1940.—The subject of the experiment was an immature male macaque weighing 2500 grams. This monkey had had the second and third branches of the right 5th nerve sectioned extradurally. In addition a lesion in the midbrain made with the Horsley-Clarke apparatus on May 8, 1940 had caused an iridoplegia in the right eye. The right pupil now reacted slightly to light; right pupil in daylight was 5.5 mm. in diameter, and when stimulated by strong light it constricted to 5.0 mm. Ether anesthesia produced marked mydriasis. Horsley-Clarke instrument adjusted under aseptic technique.

12:05.—Bipolar electrode placed at A10 L3 H-2. At rest the right pupil is 5.0 the left is 2.5 mm.

12:06.—Hypothalamic stimulation for 5 sec. Thyrotron stimulator, frequency 40 per. sec., 5 volts. Right pupil dilated to 6.5 mm. and left to 5.0 mm. There was no piloerection in face.

12:23.—Monkey was awake. Right sciatic nerve exposed for stimulation. Hypothalamic stimulations repeated with same results as above.

1:00.—Sciatic nerve stimulation with a bipolar electrode using the thyrotron stimulator caused both pupils to dilate after a short latency of 1 or 2 sec.; the right pupil enlarges from 5.5 to 6.5 mm., the left from 2.2 to 3.8 mm. There was no piloerection in face.

1:05.—Experiment repeated with same results. Right cervical sympathetic trunk exposed and stimulated with bipolar electrodes. This produces mydriasis, enlargement of the palpebral fissure and marked piloerection of the face on the ipsilateral side. The *cervical sympathetic is destroyed* preganglionically.

2:48.—Alternate stimulations of hypothalamus and sciatic nerve always produced a dilatation of the left normal pupil (from 4.0 mm. at rest, to 5.5 mm. during stimulation) but no visible change in the diameter of the right pupil which remained at 5.0 mm.

Left cerebral cortex was exposed for stimulation. A stimulus applied at a point superior to area 8 and anterior to area 6 produced a mydriasis of the left, normal, but not of the right sympathectomized iris. Hypothalamic and sciatic stimulations caused similar effects; that is, enlargement of left but not of right.

4:18.—Left oculomotor nerve was exposed and sectioned. Left pupil is now 6.0 mm. Sciatic stimulation produces a further dilatation of left pupil to 6.5 mm. but no change in right pupil. Monkey is completely out of anesthesia.

4:40.—Hypothalamic stimulation at A10, L2 and H-2. Marked dilatation of left pupil from 6 mm. at rest to 8.0 mm. during stimulation.

5:10.—Monkey is sacrificed. The left oculomotor nerve is found to be completely transected.

Brain section showed the point of hypothalamic stimulation to be at a level just rostral to the mamillary bodies, 3 mm. to the left of the midline 1 mm. ventral to the anterior hypothalamic nucleus.

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FLICKER POTENTIALS AND THE ALPHA RHYTHM IN MAN

JAMES TOMAN
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(Received for publication July 22, 1940)

INTRODUCTION

FLICKER potentials, or waves in the human electroencephalogram induced by and synchronous with intermittent visual stimulation at frequencies other than that of the alpha rhythm, were first observed and described by Adrian and Matthews (1934), who concluded that the alpha rhythm could be driven beyond its natural rate by sensory stimulation. Durup and Fessard (1935) noted that these flicker potentials were most stable at about the frequency of the alpha rhythm. Loomis, Harvey, and Hobart (1936) recorded marked flicker potentials in some human subjects, but in those having strong alpha rhythm few or no flicker potentials appeared. Jasper (1936, 1937) found flicker-following in the occipital region up to the critical fusion frequency of 40 to 50 per sec. He contended that the alpha rhythm could not be driven by flicker at frequencies other than its natural period of 8 to 13 per sec., but might be able to follow at higher rates by a process of alternation. Goldman, Segal, and Segalis (1938) considered the flicker potentials which they had recorded to be "interference patterns" between the flash rate and the alpha of repose. Jung (1939) suggested that perhaps the rhythm induced by flickering light arose from brain regions other than those producing the alpha rhythm and was not observed in most humans because of the concealed position of the optic cortex.

The present work was undertaken to investigate further the possible relationship between alpha rhythm and flicker potentials.

METHODS

The three-channel ink-writing electroencephalograph employed by Loomis, Harvey, and Hobart (1936, 1937) was made available to us through the kindness of Mr. A. L. Loomis. The time constant of the amplifiers was 0.5 sec. Frequency response was practically constant from 4–50 per sec. The noise level was less than one MV. A 5 MV input signal gave maximum pen deflection with little distortion. Experiments were usually run at one-sixth of this sensitivity.

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The subject lay abed in a screened cage with an opal glass bowl over his eyes. The bowl was uniformly illuminated over the whole visual field by a beam of light which could be interrupted at regular intervals by a motor driven sector disc. Momentary flashes of light could also be given.

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The subject lay abed in a screened cage with an opal glass bowl over his eyes. The bowl was uniformly illuminated over the whole visual field by a beam of light which could be interrupted at regular intervals by a motor driven sector disc. Momentary flashes of light could also be given.

Results

Sixty-five experiments were performed with 23 adult male subjects, and with 21 of these flicker potentials were recorded. As will be seen from Table I and Fig. 1, the subjects varied markedly in occipital per cent time alpha (Rubin, 1938) while resting quietly with eyes closed. Some showed alpha rhythm of such persistence that pattern vision of strong contrast could not block it completely. Others showed no regular rhythm under standard conditions but could be made to give occasional bursts of alpha rhythm under special conditions (hyperventilation, mild muscular activity, mild sensory stimulation, falling asleep or immediately on waking), and thus could be assigned alpha frequencies.

Table 1. Comparison of alpha and flicker activity in 21 subjects

	ALPHA RHYTHM					FLICKER POTENTIALS				
Subj.	B—% time	Freq.	Distribution			Distribution			Freq. range	Opt. freq.
			B	T	F	B	T	F		
FK	0	10.5	+	+	+	+	0	0	6.5–21.5	11
SC	0	9–12	++	++	+	++	+	0	0–22.5	9–11
JF	0	10	++	++	+	+	?	0	7.5–14	11
JT	0	12	+	+	+	+	—	—	6.8–14	11
GF	0	11	+++	++	+	++	+	0	8.5–22	10.4–10.8
NH	5	10	+	+	+	++	+	0	0–23	9–11
RS	20	11	+++	++	+	+	0	0	4–13.6	10.2–10.8
WC	26.3	10	+	++	+	+	0	0	5–21	9.3
LH	30.6	10.8	+++	++	+	+	?	0	2–18	10.5
HH	46	10	+++	++	+	+	0	0	8.7–14	10
CC	50.8	10.7	+++	++	+	+	?	0	6.8–15	10.6
GS	61	11	+++	++	+	+	0	0	9.5–19	11
JS	69	10	+++	++	+	+	0	0	5.7–15	10.4
RH	70	9.9	+++	++	+	+	0	0	8–12	9.8
CS	70	9.5	+++	++	+	+	0	0	8–15	10.3
JM	72.9	10.6	++	+	—	+	—	—	7.8–16	11
AS	75.5	11.8	++	+	+	+	?	0	9–16	11.6
BL	89.5	11.5	++	+	+	+	?	0	7–17	10.8
BS	89.5	10.2	+++	++	+	+	0	0	9–16	11
BM	94.3	9.4	++	++	+	++	+	0	8–10.2	9.8
GB	95	10.5	+	+	+	+	0	0	8.5–12	11

(B, T, and F refer to standard electrode positions on back, top, and front of head.)

Distribution of alpha rhythm and flicker potentials

In Table I the relative amount of alpha rhythm from the standard back, top, and front leads is indicated. Thirteen of 21 subjects showed greatest activity over the occipital region; 7 showed equal activity over top and back; 4 showed equal activity on all 3 leads, and in one case (WC) there was more alpha rhythm from top than back.

On the other hand, flicker potentials were particularly characteristic of the occipital region. In 10 cases they appeared only at the occipital lead; in the remaining cases they were occasionally seen also at the vertex but at lower amplitude. They were never recorded from the frontal lead. In the occipital region they were sometimes greater in amplitude than alpha rhythm

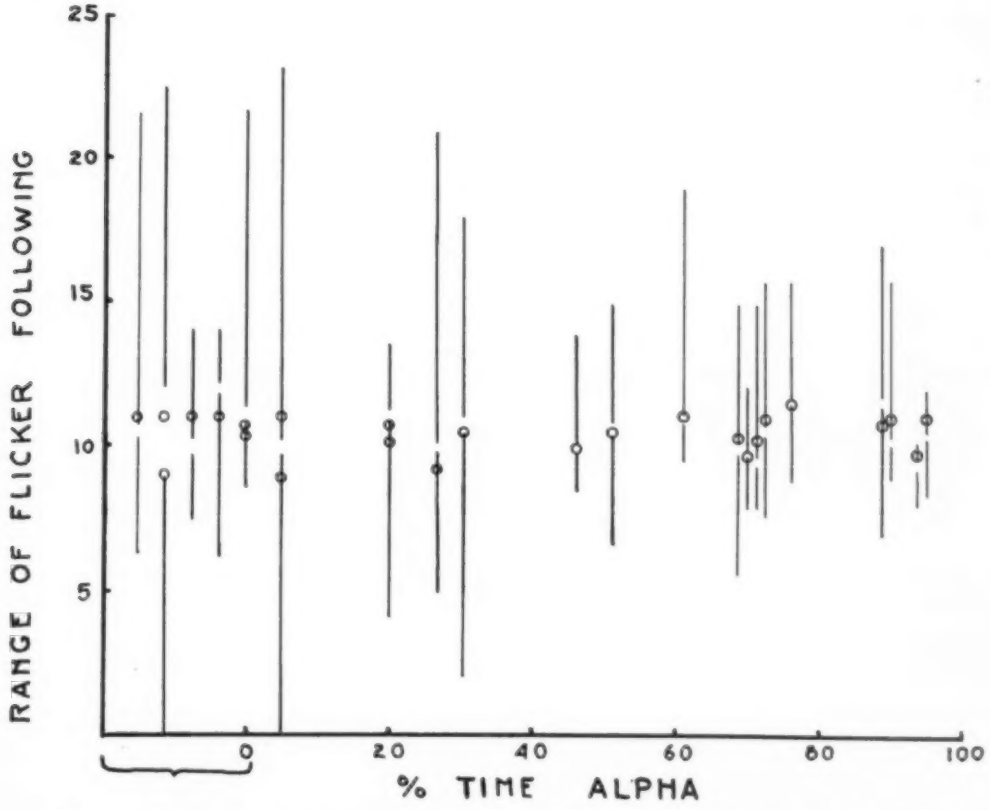

FIG. 1. Comparison of frequency range of occipital flicker potentials with regularity of alpha rhythm in 21 subjects. Circles indicate frequency of best flicker following. Breaks in vertical lines show frequency of alpha rhythm.

from the same lead. It is obvious that flicker and alpha waves do not have an identical distribution over the head.

Frequency range of flicker potentials

All 21 subjects showed at least occasional bursts of flicker-following in the region of 10 per sec. Figure 1 shows a rough negative correlation between per cent time alpha and the frequency range over which flicker potentials could be elicited. The upper limit of flicker-following was in all cases much lower than the critical fusion frequency for the same illumination, which lay between 35 and 40 per sec.

Optimum stimulus conditions for flicker-following

(i) *Flash frequency.* Table I and Fig. 1 demonstrate that the frequency of best flicker-following closely approximates the rate of the spontaneous alpha rhythm. Although maximum amplitude is indicated in the table, it will be seen from Fig. 2c that per cent time flicker (analogous to per cent time alpha) or length of bursts of flicker-following (Fig. 2a) show comparable maxima.

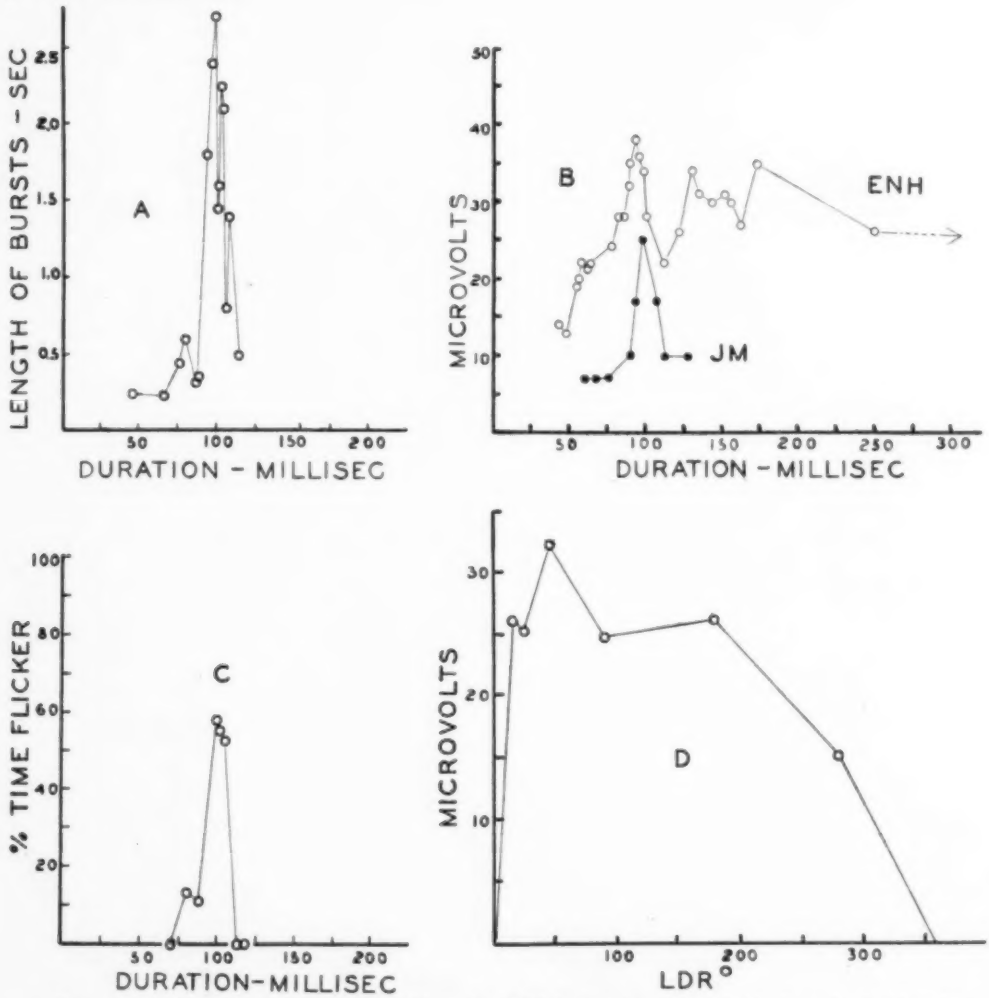

FIG. 2. A. Length (in seconds) of bursts of flicker potentials plotted against stimulus-cycle duration (reciprocal of frequency $\times 1000$) for subject GF, showing peak at about 10 per sec.

B. Best amplitude of flicker potentials plotted against stimulus-cycle duration for a low-alpha subject (ENH) and a high-alpha subject (JM).

C. Similar maximum in regularity (per cent time flicker) of flicker potentials. Subject HH.

D. Amplitude of flicker potentials with frequency kept constant but duration of light phase in each cycle varied. 360° is equivalent to continuous light. Subject ENH.

(ii) *Intensity of illumination.* The maximum brightness available over a wide field was 5 millilamberts. This was found uncomfortable by some subjects, but a reduction in intensity to 1.25 millilamberts gave a considerable loss in amplitude and regularity of response. The optimum brightness is probably higher than 5 millilamberts.

(iii) *Light-dark ratio.* Figure 2d shows the effect on flicker potential amplitude of increasing the light phase in the sector disc. A similar relation

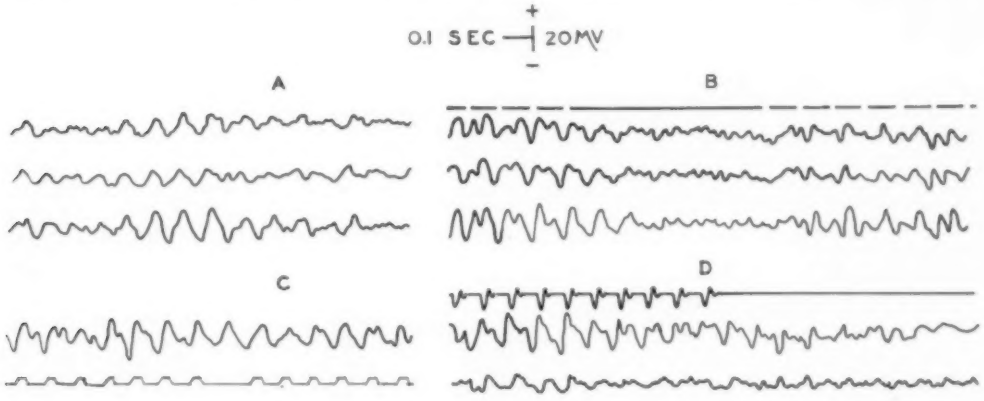

FIG. 3. Records read from left to right.

A. Short burst of alpha rhythm from three points in occipital region. Subject ENH.

B. Flicker potentials from same leads. Upper line, gaps indicate light flashes. Disorganization and reorganization of flicker response following omission of several flashes.

C. Same subject, showing no disorganization of response when only one flash was omitted.

D. Subject GF. Upper line is stimulus record, downward deflection indicating light on. Middle line, record from occipital lead. Lower line, from vertex. Flicker potentials continue for a time after last flash. Little if any following at vertex.

holds when regularity of response (per cent time flicker) is plotted against light-dark ratio. In the 3 subjects investigated the optimal light interval was found to lie between 15° and 90°.

(iv) *Size of test field.* Any reduction or irregularity in the illuminated field greatly reduced the regularity and amplitude of the flicker potentials. Occlusion of either eye, or of either lateral or medial half of the visual field of one eye, or of corresponding halves for both eyes, or reduction of the peripheral portion of the field, or occlusion of the macular portion, all gave marked reduction in response. Weak flicker potentials could be elicited when the brightest possible flicker was thrown on the closed eyelids of the subject (awake).

Response to single flashes

In some subjects Cruikshank (1937) found "on" responses to single flashes of light, but no clear "off" effects. We have observed "on" effects in only 4 subjects and no "off" effects whatsoever. The "on" response was better seen with the usual wide field than with a small intense spot of light. At

simplest it was triphasic—first phase negative and second or positive phase most marked. Usually other complications were superimposed. In subject ENH the latency was uncertain but probably less than 40 msec. (most of which time would be consumed in the retina itself—Bartley, 1934). The peak of the positive swing was reached in about 140–170 msec. ("implicit time" in the terminology of Bartley). The total response was over in about 230–260 msec. Figure 4b shows a series of responses to isolated flashes. With slowly re-

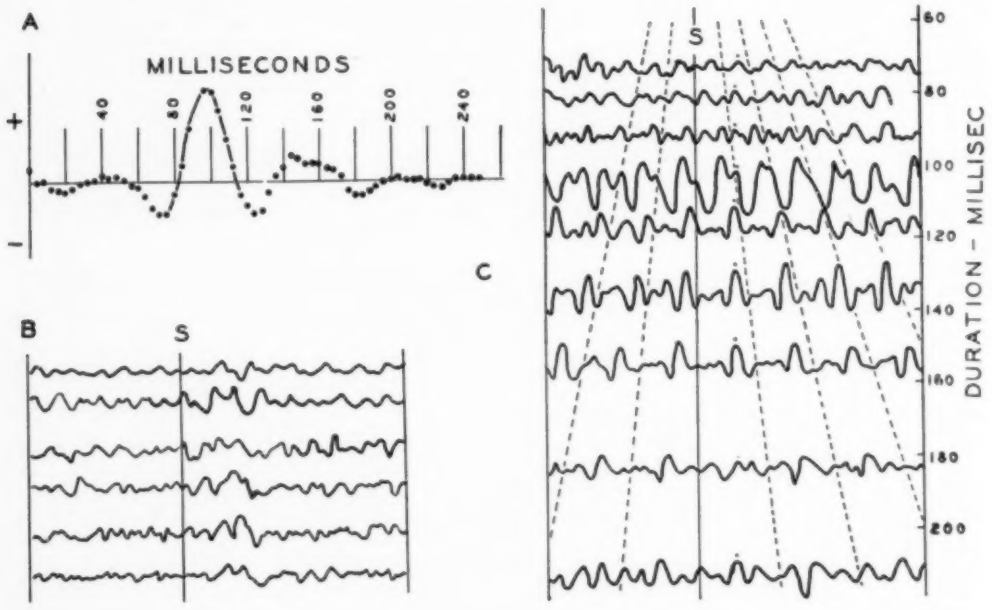

FIG. 4. Subject ENH.

A. Analysis of a number of responses to slowly repeated light flashes showing average deviation from baseline at intervals following the onset of the light flash.

B. "On" effects to isolated light flash. S, onset of light flash.

C. Flicker potentials for a series of frequencies from about 14 to 5 per sec. Radiating lines show onset of light flashes. Dots over corresponding points in response to flashes given at S. Each strip of record represents 1 sec. of activity (as also in 4B).

peated flashes (less than 4 per sec.) and the same brightness (5 millilamberts) the implicit time was reduced to less than 100 msec. An average of several such responses is plotted in Fig. 4a.

In subject ENH the "on" response was beyond the presumed limits of the area striata, but the first negative phase appeared steeper from a lead placed near the occipital pole. In subject SC an attempt was made to localize "on" responses with a small intense spot of light thrown on various points of the retina, but the responses when present were fairly generalized over the occipital region. With the usual wide field, "on" responses were seen from 5 to 0.01 millilamberts, with roughly a 10 per cent increase in implicit time for each log unit decrease in intensity.

Response to flicker

(i) *Doubling, etc.* With flashes repeated more rapidly than 5 per sec. the successive responses overlap and the chief remaining landmark is the positive peak shown by dots in Fig. 4c. The wave form may vary from roughly sinusoidal through various shades of complexity to apparent "doubling," or following at twice the flash frequency, with alternate waves sometimes unequal in amplitude; at the highest frequencies following sometimes appears at only half the flash frequency. Doubling is not characteristic of a particular frequency, nor is it characteristically absent at any point, although it appears more rarely as the upper frequency limit is approached.

Jasper (1936) has suggested that doubling may result from a succession of "on" and "off" effects. However, Fischer (1934), recording from the optic cortex of the rabbit, found only "on" effects during flicker. In the human EEG we have not seen "off" responses to light under any conditions. In flicker records we find no component with constant time relation to the "off" stimulus signal as frequency is varied. Changing the light phase of the sector disc all the way from 15 to 288° does not alter the phase relations in doubling. We are forced to conclude that the total response, however complicated, is initiated by the onset of the light flash.

(ii) *Implicit time.* For a given illumination and light-dark ratio the implicit time varied in one subject (SC) from 112 to 147 msec. over the frequency range 1 to 20 per sec., but the variation was independent of frequency. Measurements on other records failed to reveal the sort of relation claimed by Bartley (1937) for retinal response of the rabbit, in which implicit time increases up to a flash frequency of 16 per sec. and then decreases again as alternation sets in.

(iii) *Organization of the response.* Even in the most favorable subjects the flicker response does not begin maximally with the first flash of a series (Fig. 3b). At best a typical "on" response occurs to the first flash, the positive peaks attributable to later flashes then beginning at small amplitude and attaining a maximum amplitude in from 0.3 to 2 sec. Sometimes there is only irregular activity for the first few flashes, flicker-following then becoming progressively organized. Throughout a flash series there may be slow waxing and waning in amplitude accompanied by changes in wave form. This occurs in parallel fashion over the whole occipital region and is suggestive of the slow waxing and waning of the alpha rhythm seen in the resting subject. During a train of good flicker-following the omission of two or more consecutive flash causes temporary disorganization of the response. But it is sometimes possible to omit a single flash without disrupting the response (Fig. 3c), suggesting a tendency toward rhythmicity.

(iv) *Inherent rhythmicity.* This is borne out in the records of several subjects in which a decrementing train of waves was seen to continue for some time (at most half a second) after the last flash of a series. These "after-effects" were best observed at frequencies around 10 per sec. (Fig. 3c), but were also seen up to 17.5 per sec.

(v) *Localization.* Flicker-following has been recorded both lateral to the presumed boundaries of the striate area and also as far forward as the vertex, although at reduced amplitude. This might be due in part to electrical spread. However, the report of Kornmüller and Schaeder (1938) would suggest that monopolar leads far enough apart can give quite independent records, and this is supplemented by some observations of our own: (a) in 2 subjects alpha rhythm was occasionally seen at the vertex simultaneously with flicker-following of a different frequency at the occiput; (b) at times we have observed "doubling" at the occiput and single waves at the vertex, as well as the converse of this; (c) phase and frequency differences in the alpha rhythm can be recorded from the two leads. It seems certain that the flicker potentials can sometimes involve areas beyond the visual cortex proper.

It was not possible to elicit flicker potentials from one side of the head alone by illuminating only half the visual field and having the subject fixate (with either or both eyes) a point on the vertical boundary between light and dark. Several arrangements were tried, but flicker potentials occurred simultaneously on both sides if present at all.

Discussion

Flicker-following is probably a succession of over-lapping "on" responses. In favorable subjects we have been able to record a continuous progression from isolated "on" responses to typical flicker potentials as flash frequency was increased. The individual response resembles those to auditory stimulation (Davis, 1939) but is not as wide-spread as the K-complex of sleep (Loomis, Harvey, and Hobart, 1938) or similar "disturbance-patterns," which are further characterized by variable latency and long refractory period. The "on" response is not unlike that of the cat geniculate to retinal stimulation (Dubner and Gerard, 1939) or the cortical response of the rabbit (Bishop and O'Leary, 1936) and the cat (Bishop and O'Leary, 1938) to stimulation of the optic nerve. In the latter case the slowest component is not the primary cortical response but is related to one or more cycles of the spontaneous rhythm and a corresponding cycle of excitability. The rhythmicity and long duration of the human "on" response, in addition to the maximum amplitude and regularity of flicker potentials at the frequency of the alpha rhythm, leads us to believe that we are recording the activity of cortical elements like those which give rise to the slowest component of the response in cat and rabbit.

Difficulties were encountered, however, in attempting to explain the occurrence of flicker potentials at frequencies above and below that of the alpha rhythm. Flicker potentials and alpha rhythm are not proportional in their distribution over the head. Low-alpha subjects show the most stable flicker potentials over the widest frequency range. Finally, "after-effects" occur at the flash frequency rather than that of the alpha rhythm. It is hard to see how these facts can be reconciled with the "alternation" hypothesis. Nor do they necessarily lend support to the view (originally put forward by

Adrian and Matthews on the assumption that flicker potentials and alpha rhythm had a parallel distribution over the head) that the alpha rhythm can be altered in frequency over a wide range by intermittent light stimulation. It is true that synchronized potential rhythms in a small and homogeneous neurone population can be varied considerably in amplitude and frequency by a number of factors (Libet and Gerard, 1939), and such a variation, based on changes in the level of excitation, has been invoked to account for changes in human brain potentials during sleep (Blake and Gerard, 1936). But after observing the human cortical frequency spectra recorded by Grass and Gibbs (1938) and Gibbs, Williams, and Gibbs (1940), another possible explanation of the relation between flicker potentials and the alpha rhythm has occurred to us, based on the following assumptions:

(i) In the cerebral cortex there are elements capable of slow rhythmic changes both in excitability and electrical state. Such changes may be initiated either by afferent stimulation, or by the activity of neighboring elements of the same type, or may occur spontaneously.

(ii) For a given set of environmental conditions each element has a characteristic periodicity, but the elements vary as a population over a wide and continuous frequency range with typical modes (such as the 10 per sec. peak).

(iii) The greater the numerical dominance of elements of a given frequency mode, the greater the possibility of the appearance of a spontaneous synchronized rhythm at that frequency, and the less the possibility of the appearance of a rhythm arising from elements of a different natural period either spontaneously or by subcortical synchronization (as by flicker stimulation).

These assumptions would help to explain not only the inverse relation between alpha rhythm and flicker-following, but also some of the other observations mentioned earlier. For isolated flashes of light, for the first flash of a flicker series, or for flashes repeated at intervals longer than the duration of the response to a single flash, some elements of all periods might be activated by each flash in proportion to their numerical representation. But with flashes more rapidly repeated, some elements would tend to be rejected and others added to the response, depending on the relation between their natural period of excitability and the flash frequency. The most favored elements might be those of the same period as the flash frequency, or secondarily, simple multiples of it, other elements being out of step and appearing only sporadically. This sorting process might account for the progressive organization of the flicker response at the beginning of a flash series. Synchronization would be most stable at a flash frequency approximating the natural period of the numerically dominant alpha elements. Once synchronized, a group of elements might be able to continue rhythmically by mutual interaction for a time after the cessation of the flicker stimulus, giving rise to the "after-effects" noted. The stimulus conditions most favoring synchronization would be those insuring the arrival of the largest burst

of impulses simultaneously over the widest portion of the striate area—thus the necessity for the widest possible visual field simultaneously and evenly illuminated. Synchronization would be most probable in the immediate region of projection of the optic pathways, but might spread somewhat beyond these limits by interaction with similar neighboring elements.

Until more refined methods can tell directly whether a change in flash frequency brings about either a frequency change in individual cortical neurones (the population being homogeneous) or a change in the type of neurones responding (the population being heterogeneous), we are inclined to think that our observations fit more easily into the latter concept.

Summary

Flicker potentials in response to intermittent light stimulation were observed in the electroencephalograms of 21 subjects. Subjects having a low per cent time alpha rhythm showed the widest frequency range of flicker-following. In amplitude and regularity flicker potentials were best at about the frequency of the alpha rhythm. They were confined to the occipital region except for occasional appearance at the vertex. They were found to require a period of time for organization at the beginning of a train of flashes. Once organized, they showed an inherent rhythmicity and could continue for a short time after the cessation of the stimulus. "On" responses to isolated light flashes were observed in some subjects, but "off" responses were never seen and are considered to be absent even in the phenomenon of "doubling."

Flicker-following is interpreted as a succession of over-lapping "on" responses comparable to the slowest components of the cortical response to optic nerve stimulation studied by Bishop and collaborators in the cat and rabbit. It is suggested that the cortical elements involved include not only some of those whose spontaneous activity may be recorded as the alpha rhythm but also others of different natural frequency which are ordinarily prevented from synchronization by the dominant alpha rhythm.

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EFFECTS OF PREFRONTAL LOBOTOMY ON DEPRESSED PATIENTS

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THE OPERATIVE procedure of prefrontal lobotomy was carried out on a small group of patients with severe depression, agitation, and apprehension, to ascertain whether relief could not be obtained from their symptoms, and, at the same time, to determine whether the operative procedure affects the mental abilities of these psychotic individuals. The operative procedure, as previously outlined by one (9) of us, consists of cutting across the long association fibres in each prefrontal lobe, just anterior to the tip of the anterior horn of the lateral ventricle. Some of the superficial short association pathways may be sectioned by this procedure but some of them probably escape, while all the deep association pathways are believed sectioned on both sides. In two of the patients in the series the operation was unilateral, the left in one patient, the right in the other. Our operative procedure is more complete and probably more effective than the operation described by Moniz (10) and used by Freeman and Watts (4). Since our operation is under direct visual control we are more certain of the fibres cut and we can therefore more accurately appraise the patient's behavior and mental reactions before and after operation.

We realize certain inherent difficulties in a study of this kind because we are dealing with mentally ill individuals whose behavior prior to the operation is conditioned by the psychotic process and thus the individual's capacities and abilities may not be reliably determined by the psychometric examinations. Lack of coöperation, whether of psychological or of physiological origin, malingering, interfering mental trends, will impair the validity of the psychometric results.

We have studied both the therapeutic and the psychological effects of the operation, but are aware that valid generalizations can not be made in certain spheres because certain variables can not be controlled. In addition, the therapeutic results are difficult to estimate because, as yet, there are no objective criteria for evaluating social recovery. Therapy in mental illness can not be measured as objectively as in physical disorders. If a patient's condition changes from an extreme depression to a hypomanic condition, can any conclusions be made concerning the extent of social recovery? Perhaps if those patients are discharged who are considered hypomanic, is it not possible that they may become socially adjusted? Also how can one determine whether the social efficiency that results is equal to the efficiency level prior to the psychotic process? Babcock (2) has attempted to measure mental deterioration, and her results indicate that there is definite correlation between the amount of mental deterioration and lack of social adjustment.

We have tried indirectly to secure some index of this deterioration but the indices secured are only rough indications of 'mental efficiency.' In addition the efficacy of the operation may be affected by the duration of the psychosis; and controlled experimentation may reveal the importance of this factor. Thus Jelliffe and White (8, see p. 1092) report that 40 per cent of the cases of involutional melancholia recover.

All the patients selected for the operation were diagnosed by the staff to be either manic-depressive psychosis in an agitated depressed condition or involutional melancholia. During the week preceding the operation, the psychologist attempted to administer the Stanford-Binet examination to patients thus selected. After the operation frequent notes were made about the patient's condition by the hospital surgeon. About a month later, when the patient's condition permitted, the psychologist retested the patient. If because of unimproved condition the patient remained in the Hospital further notes were made by both attending physician and occupational therapist. If the patient was furloughed home, a letter from the guardian kept us informed of the progress.

The physicians and the occupational therapist were not influenced by the psychometric results since at no time were these results revealed to anyone. The testing was done in the psychologist's office, and the patient was not told that the tests would be repeated. The inability of the patient to discuss the examination with anyone, the psychotic condition, and the fact that a surgical operation followed the psychological examination, all tended to eliminate the practice effect due to a retest.

Up to the present date there were 13 cases at the Florida State Hospital on whom prefrontal lobotomy operations were performed. It was not possible to secure psychometric examinations on all these cases but detailed progress notes have been secured. Social case histories were obtained with the coöperation of the District Social Welfare Workers.

Because the depression tended to change to a condition of hypomania after operation, it was thought that a prefrontal lobotomy on one lobe only might lessen this tendency. Thus on 2 of the 13 patients the operation was performed only on one lobe—the left lobe on one patient and the right on the other.

The following are some of the observations: (i) *Emotional tone after operation*. One of the most striking changes noted in these cases after, as compared to before, operation was the emotional tone. All 13 patients with an agitated depression became more normal in their emotional expressions after the prefrontal lobotomy. Lyerly (9) performing a prefrontal lobotomy on 7 cases in private practice reports similar results. Freeman and Watts (4) operating on 6 psychotic individuals concluded that there was a substratum, a common denominator of worry, apprehension, anxiety, insomnia, and nervous tension; and in all of them these particular symptoms were relieved to a greater or lesser extent. In a later article Freeman and Watts (5) reported similar results on a group of 20 cases.

(ii) *Subsequent course of the emotional tone.* The subsequent course of the emotional tone is not similar in all 13 cases. Seven of the patients became so excited, disturbed and hyperactive, that they had either to be kept in the institution or returned to the hospital after they had been furloughed. The others were either still home on furlough and getting along well, or else had remained in the hospital as depression developed. It may be noted that the depression persisting some time after the operation was less severe than prior to the prefrontal lobotomy.

(iii) *Intellectual changes.* An interesting problem presented by such operative procedure concerns the intellectual functions of the prefrontal lobes. The question naturally arises whether cutting nearly all of the association fibres in the white matter of both prefrontal lobes affects certain intellectual capacities. Only precise psychological testing with adequate controls and strict adherence to the scientific method can yield valid answers. In the present study our difficulties were further increased because the operation and the psychometric testing had been done on psychotic, not normal, individuals.

One method of studying the effects of a prefrontal lobotomy on the intellectual functions would be to compare the test results following the operation with those preceding the operation. Psychometric examinations were not secured on 8 of the patients both before and after operation; and thus we are limited to a study of 5 cases.

In all these cases, the reexaminations after the operation yielded almost identical results to each individual test item as compared to the original tests prior to the operation. The slight changes were not significant or consistent.

Spurling (13) reported a case in which he resected the right prefrontal lobe in the case of a tumor which had already destroyed most of the left prefrontal lobe. Ackerly (1), reviewing this case, concluded that the patient's intelligence, reasoning, and judgment had not been disturbed. Freeman and Watts (5) report as a result of a prefrontal lobotomy on 6 psychotic patients that the memory was not obviously impaired and concentration was improved, possibly on account of the relief of the preoccupation. Judgment and insight were apparently not diminished and the ability to enjoy external events was certainly increased. Goldstein (7) says that in patients with lesions of the prefrontal lobes abstract behavior is lacking, but concrete behavior may be well preserved. Brickner (3) reported a case in which there had been an extensive resection of both prefrontal lobes for brain tumor. His studies based on this single case would indicate that there was considerable impairment of mental function. Fulton and Jacobsen (6) report an absence of distractability in carrying out a test problem after operations on the prefrontal lobes in apes. Rylander (12) in a clinical study of operations on the frontal lobes in 32 cases using a matched normal group suggested that the clinical group showed considerable impairment of immediate memory, was inferior to the normal group in the retention of word associations and in

nonsense syllable learning, but not in the learning of word-associations or in syllable and digit memory span. All operations in these cases were really concerned with frontal lobe tumors.

(iv) *Deterioration and analysis of individual test items.* Using as criteria of deterioration the "scattering," failure of tests markedly below the patient's intellectual level as measured by the Terman Vocabulary and the difference between the Binet Age and the Vocabulary Age, we note that all 10 patients tested after the operation had deteriorated to a greater or lesser extent. The frequency of the failures on the Stanford-Binet Intelligence Examination between the years 9 and 12 inclusive after the prefrontal lobotomy for the ten patients tested are given in Table I.

Table 1

Year	Test items	Frequency of failures
9	Date	1
	Weight	6
	Making change	0
	Reversed digits	3
	Sentences	1
	Rhymes	5
10	Vocabulary	0
	Absurdities	3
	Designs from memory	7
	Reading	2*
	Comprehension	2
	Free association	9
12	Vocabulary	0
	Definitions	1
	Ball and field	5
	Dissected sentences	1†
	Fables	8
	Reversed digits	6
	Picture interpretation	8
	Similarities	7

* Test omitted on 2 patients.
† Test omitted on 3 patients.

To what extent these results are due to the psychotic process or to the prefrontal lobotomy might be a matter of controversy. The 5 tests that were secured prior to the operation on the 5 patients mentioned above showed that similar deterioration test results were indicated by subtracting the Binet Ages from the Terman Vocabulary Ages. The failure on the individual test items again demonstrated that the deterioration, if actually present, was not a result of the prefrontal lobotomy.

(v) *Free association test.* A significant fact was observed in the test of "free association" on year 10 of the Stanford-Binet Intelligence Examination where the patient is asked to name as many words as possible during a 3-

minute period. Credit is obtained if at least 60 different words are named. Of the 10 patients tested after operation all but one failed this test. The patients would start naming a few words, then stop, laugh, in an embarrassed manner, and refuse to continue. They would frequently insist that they did not know any more words. Of the 5 patients tested prior to the operation, four had passed this test before the prefrontal lobotomy, and three failed the test afterwards.

No explanations are suggested for this observation but it must be noted that the operation does cut the association fibres, and that this test is supposed to test association.

In order to determine whether the test results secured immediately after the operation were reliable, we again retested 4 of the 10 patients examined. These 4 patients all failed the free association test and the test results indicate very little change.

(vi) *Delusions and hallucinations.* No conclusions can be made concerning the presence or absence of delusions and hallucinations after operation. Seven patients definitely expressed delusions of persecution prior to operation and three of these patients still expressed their delusions after operation. In the 2 cases where hallucinations were elicited previous to prefrontal lobotomy, one still had these hallucinations after the operation.

(vii) *Other personality changes.* After operation it was noted that the patients tended to reminisce. During the psychometric examinations some stimulus word in the directions would result in the patient describing some past experience. It was necessary for the examiner to interrupt trend and bring the patient's attention back to the examination.

(viii) *Right and left prefrontal lobes.* In 2 of the cases, prefrontal lobotomy was done on one lobe—the left prefrontal lobe in one case, and the right prefrontal lobe in the other. One of these patients has been sent home and is apparently getting along well. The other patient is still in the hospital and expresses various bodily complaints. As yet, valid conclusions can not be made.

Summary

From a study of the behavior of 13 patients undergoing a prefrontal lobotomy operation for a depressed condition, we note a definite heightening of the emotional tone. The subsequent course of this emotional change varies but there is a tendency to remain above the level of depression that characterized the patients prior to the operation. The psychometric tests did not reveal any significant changes in the intellectual abilities. The efficacy of the operation should not be determined from the present study because of the lack of a control group and the difficulty of objectivity defining social recovery. Studies of those patients who had a history of previous mental attacks do not reveal any trends distinct from those patients who had no former mental upsets.

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SYMPATHETIC PREGANGLIONIC OUTFLOW TO LIMBS OF MONKEYS*

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INTRODUCTION

THE WIDE adoption of sympathectomy in the treatment of vasomotor disease has necessitated a more precise knowledge of the anatomy of the sympathetic pathways, particularly in the thoracic and lumbar regions. The present scheme of the outflow of the preganglionic nerve fibres to the limbs is based largely on the early experiments of Langley[6,7,8,9,10] and Bayliss and Bradford[2], who used erection of hairs, sweating, or vascular changes for recording sympathetic activity. These types of effector activity do not lend themselves readily to quantitative estimation. Moreover sweating and vasomotor changes offer additional difficulties in that they are complex responses. Sweating is influenced by accompanying vascular changes, while vasomotor effects in turn are subject to rapid modification by compensatory reflexes.

In the present experiments a direct insight into the kind and magnitude of the sympathetic nerve impulses themselves was obtained by recording the action potentials in the efferent nerves. A direct current amplifier, which Marrazzi[11] had found, in recording action potentials from other parts of the sympathetic system, to be especially suitable, was utilized to actuate a Matthews oscillograph.

Langley, and Bayliss and Bradford worked on cats or dogs, animals which possess usually 13 thoracic and 7 lumbar spinal nerves, and there has been considerable difficulty in translating the results of the experiments in terms of man. Up to the present the anatomy of the sympathetic pathways to the limbs has never been investigated in primates, Ascroft's interpretation of his important studies[1] on adrenaline sensitivity in the monkey following "pre-" and "post-ganglionic" division having been based on Langley's analysis of the cat. The Rhesus monkey (*Macaca mulatta*) has therefore been utilized in the present study. It normally possesses 12 thoracic nerves as does man.

In our early experiments on the lower limb, when the method was being tested and proved, cats were used, so that it was possible to check by this new technique the outflow, as determined by Langley through observations of vasomotor changes and sweating. The results of this part of the investigation have been presented in a preliminary communication (Sheehan and Marrazzi[13]).

METHOD

Under light nembutal anesthesia (dose 32 mg. per kg.), a tracheal cannula was tied

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in place and a laminectomy performed. Several spinal nerves, usually three or four in each experiment, were prepared by severing them from the cord and excising the dorsal root and ganglion. After insulation from surrounding tissues, the distal cut end of the ventral root was stimulated by accurately controlled shocks from a thyratron stimulator. These were usually maximal or supramaximal. A rate of 2 per sec. was used to avoid additive effects between successive shocks (Marrazzi[11]), and thus make the length of the period of stimulation unimportant. When this was controlled and the rate was varied up to 40 per sec. the results did not differ from those presented.

The activity resulting in the peripheral nerves of the limb in question was detected by electrodes, placed on the main branches, and connected to the amplifier (Fig. 1). The

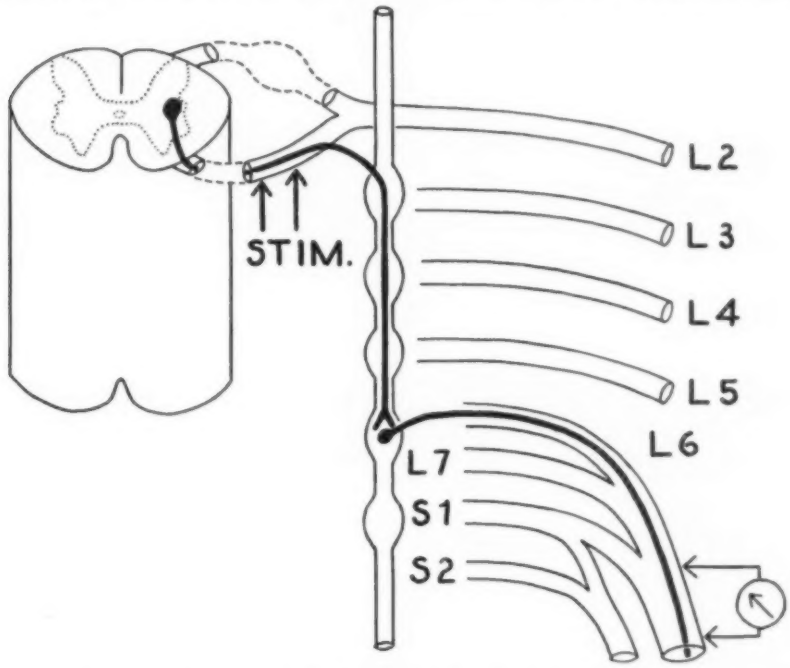

FIG. 1. Diagram showing site of stimulation of distal cut end of ventral root and of recording from sciatic nerve in the thigh.

C and B waves thus recorded enabled the mapping of the exact roots through which sympathetic fibres passed to the limbs, and by recording from the contralateral side data were obtained on the extent of extraspinal crossed pathways in such outflows. With a conduction distance of 15–35 cm. and a camera speed of 7 cm. per sec., a good separation was obtained between the B and C waves, while A waves would have been incorporated (though still discernible) into the end of the shock artifact.

Since all slowly conducting fibres are not necessarily autonomic, the possibility that some of the C and B waves might have originated elsewhere was considered and excluded by the fact that the intravenous injection of nicotine, which in the doses given (10–30 mg.) acts at autonomic ganglia without affecting postganglionic or somatic nerve trunks, was effective in blocking the previously recorded impulses. This eliminated any slowly conducting somatic efferents as a source of the potentials. It also constituted a check that any current spreading along the ventral root did not stimulate the distal cut stump of the dorsal root, and initiate an antidromic impulse in a slowly conducting afferent fibre. Existing anatomical knowledge indicates that the majority of roots stimulated do not contribute afferent or somatic efferent fibres to the limbs.

The good muscular responses obtained indicated that the animals were in good condition. When the muscle contraction interfered with the recording it was eliminated by cutting of appropriate nerves. At the termination of each experiment the roots stimulated

were checked by autopsy, at which time the total number of thoracic and of lumbar vertebrae was noted (later checked by x-ray), and a dissection made to record the exact fixation of the lumbo-sacral plexus, according to the definitions given by Sherrington[14] and by Zuckerman.[16]

Results

Cat (Lower limb). The findings in the cat have already been presented in some detail in the preliminary note and are summarized here in condensed

COMPARISON OF SYMPATHETIC PREGANGLIONIC OUTFLOW TO THE LOWER LIMB IN CAT AND MONKEY

CAT					MONKEY		
No. of Exp.		Positive Responses C or B waves	Root	No. of Exp.	Positive Responses C or B waves		
1		0	T 7				
1		0	T 8				
3		0	T 9				
4		0	T10	3	0		
9		1	T11	3	1†		
8		2	T12	3	2		Total Outflow
7		4	T13*				
6	Major Outflow	6	L 1	3	3	Major Outflow	
9		9	L 2	6	6		
4		2	L 3	5	5		
3		1	L 4	3	0		
2		0	L 5	3	0		
2		0	L 6	1	0		
1		0	L 7	1	0		

Total Outflow

Fig. 2. Table of results in cat and monkey (lower limb).

* No T13 root in the monkey.

† Only 11 thoracic roots in this animal.

tabular form (Fig. 2). The results show that the preganglionic outflow to the lower limb via the sciatic nerve emerges from the spinal cord by the ventral roots of T11–L4 (inclusive) and that the roots giving the greatest contribution are T13–L3 (inclusive) of which L1 and L2 invariably give a response. T11 rarely contributes and T12 and L4 only occasionally.

From the positive roots B (10–20 m. per sec.) and C (1–2 m. per sec.) waves, or C waves alone, were recorded. The C waves appeared in all cases except two where the animal was in poor condition. In these apparently only the fibres of lower threshold responded, giving B waves alone. When the stimulus elicited both B and C waves, the B wave was much smaller in both height and area than the C wave as shown in Fig. 3 where, following each

sharp downward deflection, which is part of the stimulus artifact, appear a small B and a large C wave. These are indicated at the beginning of the record by an arrow and the letters B and C respectively. Nicotine injected intravenously in doses of 10–30 mg. blocked both C and B waves from these roots. Complete abolition by nicotine of the responses from L1 is seen in Fig. 3.

Recording from the medial and lateral popliteal divisions of the sciatic nerve separately gave the same result as recording from the combined nerve. No responses from the contralateral sciatic nerve were ever obtained, if care was taken to avoid spread of current. Crossed pathways, between the sym-

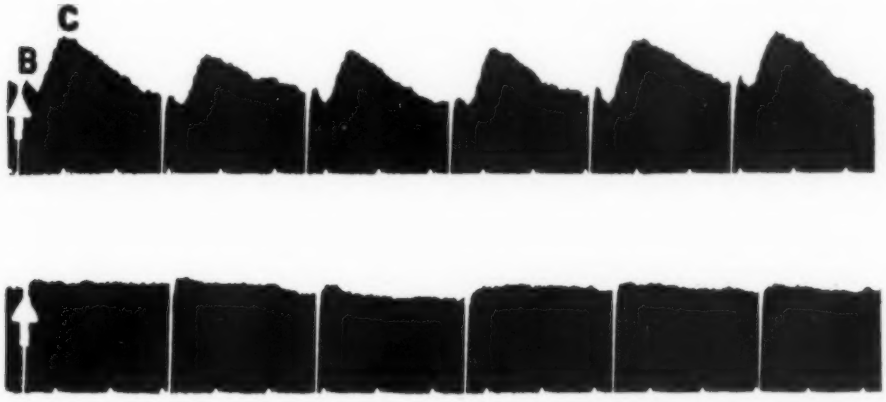

FIG. 3. Effect of nicotine on sympathetic potentials of cat's sciatic nerve. Postganglionic responses on stimulating ventral root of L1 *before* (UPPER LINE) and *after* (LOWER LINE) injection of 10 mg. of nicotine. ↑ =stimulus artifact; B=B wave; C=C wave; time in $\frac{1}{5}$ sec.

pathetic chains, of fibres destined for the opposite sciatic nerve were therefore not demonstrated.

Monkey (Lower limb). The results for the monkey have been tabulated and placed alongside those of the cat for comparison (Fig. 2). Stimulation of T10 gave no response. C waves appeared only once on stimulation of T11 and this animal turned out to have 11 thoracic and 7 lumbar vertebrae, so that T11 was the last intercostal nerve. Stimulation of T12, L1, L2 and L3 gave C ($\frac{3}{4}$–1 m. per sec.) responses in all experiments, the responses from T12 being smaller in amplitude than those from the lower roots. In addition small B (8 m. per sec.) waves, which were not nearly so conspicuous as they had been in the cat, were occasionally obtained. Stimulation of roots below L3 never yielded sympathetic potentials. The outflow of preganglionic fibres to the lower limb in the Rhesus monkey would therefore appear to be from T12–L3 (inclusive), with T11 participating under exceptional circumstances, and T12 giving a smaller contribution than the other roots. Thus whereas 7 spinal roots in the cat participate in the preganglionic outflow to the inferior extremity, only 4 roots contribute in the monkey. The outflow in the monkey

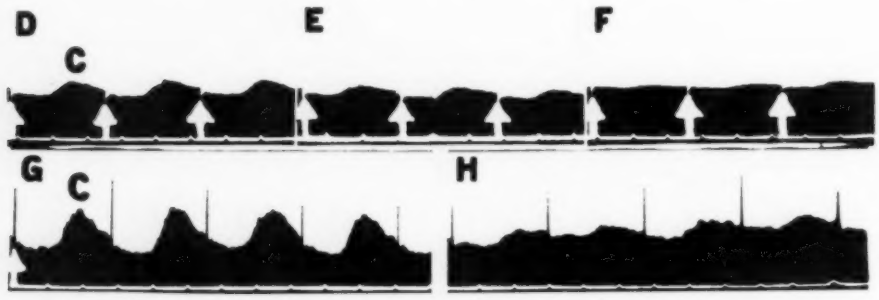

FIG. 4. Effect of nicotine on sympathetic potentials of monkey's sciatic nerve. Postganglionic responses on stimulating ventral roots of L3. Upper line (D E F) = low gain; Lower line (G H) = high gain D & G before E immediately after injection of 10 mg. of nicotine, and F & H 5 min. later. ↑ = stimulus artifact (reversed in GH) C = C wave; time in $\frac{1}{5}$ sec.

is therefore more restricted. Nicotine injected intravenously in doses of 10–30 mg. blocked the responses from these roots. Figure 4 shows the effect of 10 mg. of nicotine on the C wave obtained by stimulating L3. The upper line, taken at lower gain, shows an immediate reduction in response after nicotine (E), and a more complete block five minutes later (F). The lower line shows a higher gain record of the control (G), and the degree of block five minutes after the injection of nicotine (H).

As in the cat, no responses were obtained from the contralateral sciatic nerve. There appears therefore no evidence substantiating the belief that

Ventral Root	No. of Exp.	Positive Responses (C or B) Total			Analysis of Positive Responses					
					Median Nerve		*Ulnar Nerve*		*Radial Nerve*	
					No. of Exp.	Positive Responses	No. of Exp.	Positive Responses	No. of Exp.	Positive Responses
C 8	1			0	1	0	1	0	1	0
T 1	2			0	2	0	2	0	2	0
T 2	3			0	3	0	3	0	3	0
T 3	4			0	4	0	4	0	4	0
T 4	4			2	2	0	3	2	4	2
T 5	6	Total Outflow	Major Outflow	6	3	3	4	4	6	4
T 6	5			5	2	2	5	5	4	4
T 7	4			4	2	2	4	4	4	4
T 8	4			3	2	1	3	2	4	2
T 9	3			0	3	0	3	0	3	0
T10	2			0	2	0	2	0	2	0

Fig. 5. Contribution of sympathetic potentials from thoracic ventral roots to the upper extremity in the monkey

functional pathways to the lower limb cross between the sympathetic chains. Recording from the medial and lateral popliteal divisions of the sciatic nerve separately gave the same result as recording from the combined nerve, and this also agrees with the findings in the cat.

Monkey (Upper limb). The outflow of sympathetic preganglionic fibres to the upper limb was confined in the monkey to T4–T8 (inclusive), with the major outflow coming from T5, T6, and T7 (Fig. 5). The contributions from

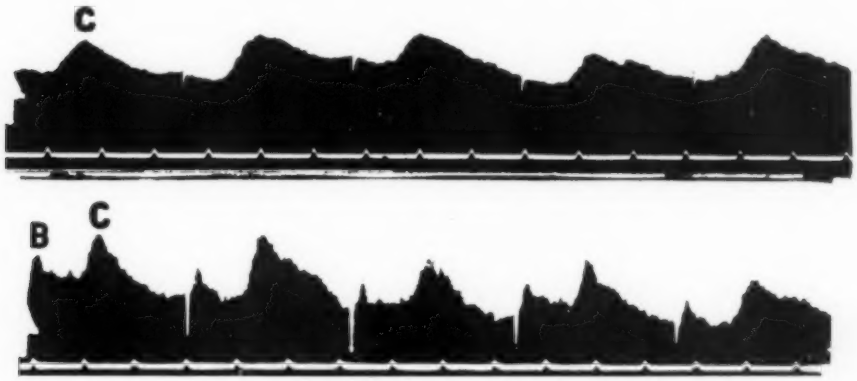

FIG. 6. Sympathetic potentials in the arm (monkey). Upper line—C waves in ulnar nerve on stimulating ventral root of T6. Lower line—B and C waves in median nerve on stimulating ventral root of T7. ↑ =stimulus artifact; B = B wave; C = C wave; time in $\frac{1}{5}$ sec.

T4 and T8 were less constant and smaller in magnitude. From above T4 and below T8 sympathetic potentials were never obtained in the nerves of the arm. There appeared to be no definite difference in the *extent* of total outflow to the median, ulnar and radial nerves. Variations in the fixation of the brachial plexus did not seem to have any bearing on the extent of outflow.

All the positive roots gave C ($\frac{3}{4}$–1 m. per sec.) waves (Fig. 6). Occasionally a B (8–10 m. per sec.) wave was also recorded from the ulnar and median nerves. The lower line in Fig. 6 shows an unusually good example of B waves. Only once was a small B response picked up from the radial nerve. Nicotine in doses of 10–30 mg. injected intravenously blocked the sympathetic responses in the median, ulnar and radial nerves from stimulation of the positive roots.

All the monkeys, except one, proved on autopsy and x-ray examination, to possess the usual number of thoracic (12) and lumbar (7) vertebrae. In one monkey where there were only 11 thoracic vertebrae and the usual number of lumbar, the outflow to the lower extremity extended up as far as T11, the last intercostal nerve in this instance. The variations in the fixation of the lumbo-sacral and brachial plexuses were not associated with any obvious differences in the preganglionic outflows to the limbs.

Discussion

Langley's work[6,7,8,9,10] was carried out exclusively on cats under chloroform and ether anesthesia. For the lower limb he stimulated T10–L4 (inclusive) and observed the sweat formed on the pads of the feet. Although variations existed, the maximum number of sudomotor fibres emerged in L1 and L2, some in T13 and still fewer in T12 and L3. In a later paper (1894) he added a contribution from L4 in animals with a "posterior" type of (post fixed) lumbo-sacral plexus, but there appeared no constant relation between the arrangement of the plexus, and the position of the uppermost nerve containing secretory fibres for the lower limb. In a study of the vasomotor nerves to the limbs Langley reported that the maximum pallor occurred in the hind foot from stimulation of T13, L1 and L2, and in his later paper (1894) he extended the outflow of vasomotor fibres to the inferior extremity to T12–L4; only once did he note any vascular change on stimulation of T11. In the fore-foot of the cat he obtained profuse sweating by stimulation of T6, T7, T8 and slight sweating on stimulation of T4, T5 and T9. The largest sudomotor outflow occurred in T7. Vasomotor effects were obtained from the same roots, the sudomotor and vasomotor outflows coinciding very exactly. In the fore-foot then no vascular or secretory effects were ever observed by Langley following stimulation of roots above T4.

Bayliss and Bradford[2] adopted the plethysmographic method for recording vascular changes in the limb. Dogs under chloroform anesthesia and curare, and with the plethysmographic cuff reaching above the middle of the thigh, showed vasoconstriction in the lower limb from stimulation of the spinal roots from T11–L3 inclusive. It was least effective from T11 and L3. Stimulation of T10 and L4 had no effect. With the exception of the absence of any contribution from L4 their results corresponded closely with those of Langley in the cat. In the fore limb of the dog with the plethysmograph extending as high as the axillary folds, Bayliss and Bradford recorded a reduction in volume of the limb following stimulation of T4–T11 (inclusive), and found the maximum result occurring after stimulation of T6, T7 and T8. Stimulation of T2 had no effect. Stimulation of T3 only occasionally produced a slight diminution in volume of the limb. Stimulation of T11 gave slight diminution in volume of the upper limb only after the splanchnic nerves had been cut, which eliminated the predominant pressor effect from vasoconstriction in the visceral bed.

Our results in cats agree closely with these analyses of Langley, and Bayliss and Bradford based on the outflow of sudomotor or vasomotor fibres to the lower limb. In the Rhesus monkey the outflow appears to be restricted to fewer spinal nerves. This may perhaps be related to the assertion that the that cat is more sympathicotonic than the monkey, although it is quite possible the results do not indicate a smaller outflow but only a condensation.

Derom[3] (1938), working in Heyman's laboratory, has utilized the carotid sinus reflex for recording vasomotor changes in the lower extremity. In dogs

under chloralose anesthesia, the pressures in the femoral artery and vein, and carotid artery were recorded manometrically. Section of the rami communicantes of the upper three lumbar nerves abolished the vasomotor effects in the corresponding lower limb ordinarily initiated by the carotid sinus reflex. Derom therefore restricts the outflow of preganglionic fibres to the inferior extremity to these three spinal roots, although he did not determine whether it was necessary to cut all of these. His results fall within the major outflow we describe, but his method is probably not sensitive enough to define the limits of the total outflow where the roots afford only weak contributions.

An emergence of vasomotor fibres from the lowest lumbar segments to the inferior extremity is suggested by the observation of Oughterson, Harvey and Richter[12]. They found that ligation of the femoral artery in the dog caused a fall in skin temperature which remained for several hours and was followed by a spontaneous rapid rise in temperature, indicating the opening up of collateral circulation. Since removal of the sympathetic supply hastened the return of skin temperature to previous levels, they concluded that vasoconstriction is a factor in the initial fall and that a procedure like transection of the cord, which also offsets the temperature drop, is a good test for the detection of the level of exit from the cord of vasocontrictor pathways. Utilizing this test Oughterson, Harvey and Richter found that transection of the spinal cord as low as L6, three to four hours after ligation, was followed by vasodilatation in the lower extremity. Presumably section at this level severed vasoconstrictor pathways descending within the cord to emerge below L6. There are many factors, however, entering into this indirect method of estimation. One misses, therefore, the decisive indication of validity that would have been afforded by the comparison in each animal of the simultaneous changes taking place in an unligated control limb with those in the ligated limb after cord transection.

The upper level of the outflow to the superior extremity in man is of special significance in planning any operation designed to divide only preganglionic fibres. It is particularly unfortunate that precisely here there should be lack of exact anatomical knowledge. The findings in the monkey as outlined in the present study do not admit the acceptance of preganglionic fibres destined for the upper limb emerging from the spinal cord above T4. The results are in close accordance with the analyses of sudomotor and vasomotor pathways to the upper limb as stated by Langley, and Bayliss and Bradford. It is worthy of note that Sherrington[14] in his studies of the lumbosacral and brachial plexuses of the monkey did not mention any vascular changes in the upper extremity upon stimulation of the ventral roots of T1, T2 or T3 although special attention was paid in these experiments to sympathetic effects. Excitation of T1 in addition to movements of the fingers and wrist produced *only* dilatation of the pupil. Excitation of T2 and T3 in addition to somatic motor responses produced dilatation of the pupil, opening of the palpebral fissure, erection of hair on the scalp, erection and paling

of the pinna, and vasoconstriction in the lateral lobe and one half of the isthmus of the thyroid gland.

Kuntz, Alexander and Furculo[5] however believe that preganglionic neurons involved in the sympathetic innervation of the upper extremity are located in the upper thoracic region of the spinal cord, beginning with the first thoracic segment and extending downwards at least as far as the third or fourth segment. They base their belief on experimental histological evidence and also upon observations following stimulation of the ventral roots of these spinal nerves. In cats unilateral section of the roots of T1 was followed two to three weeks later by complete degeneration not only of the preganglionic fibres entering the stellate ganglion through the white ramus of this nerve, but also of the major portion of the inter-cellular fibre-complex in the portion of the ganglion adjacent to this ramus, and they add "the number of ganglion cells with which preganglionic components of the first thoracic nerve effect synaptic connections obviously is large. The *distribution** within the ganglion of the axons arising from these ganglion cells, furthermore, indicates that many of them enter gray rami which join the nerves which make up the brachial plexus." Such evidence is however inconclusive in view of the present inadequate knowledge in regard to the location of the post-ganglionic cells related to the limbs.

Kuntz, Alexander and Furculo[5] however report sweating in the pads of the fore-foot on stimulation of the ventral root of either T1, T2 or T3, and also a constriction of the ulnar artery when exposed in a distal part of the extremity. These findings are entirely at variance with previous observations and we are inclined to believe that there may have been some unobserved spread of stimulating current, a complicating factor which in such experiments is one of the most difficult to eliminate.

Smithwick[15], from his extensive clinical experience, believes that in man there may be sometimes a sympathetic outflow from the second and third thoracic segments to the upper extremity. He claims that, in the treatment of vascular spasm of the hand, in addition to section of the sympathetic chain below the 3rd thoracic ganglion, division of the spinal roots of T2 and T3 should be performed, holding that section of these roots instead of their rami (as in Telford's operation) offers surer prevention of regeneration. The findings in the monkey recorded above cannot of course be transferred directly to man, but the fact that the outflows of preganglionic sympathetic fibres to the extremities in cat, dog, and monkey, are so nearly the same, implies a similar arrangement in man, and the more restricted outflow in the monkey would lead one to expect a narrower rather than a more extensive outflow in man.

Crossed pathways between the sympathetic chains certainly exist as an anatomical possibility. Langley has shown that in the cat, one at least of the sacral ganglia is connected by transverse strands with the corresponding

* The italics are ours.

ganglion of the opposite side, and sometimes the first sacral ganglia on the two sides form one fused median ganglion. The transverse connections, according to Langley, serve largely the purpose of connecting the lumbar white rami on each side with both sides of the pelvic viscera, but he also found some evidence of crossed pathways to the lower limb. By stimulating the peripheral cut end of the sympathetic chain above the sixth lumbar ganglion, he observed slight sweating on the opposite foot on a few occasions, and concluded "that either a few preganglionic fibres cross to the ganglia of the opposite side, or some of the post-ganglionic fibres of one side run to the opposite grey rami."[10] The question of such crossing has gained new significance in view of the clinical finding that after *unilateral* lumbar sympathectomy *both* lower extremities show an initial marked rise in skin temperature. The results of the present experiments show that neither in the cat nor in the monkey can such pathways be detected. The explanation of the vasodilatation in the contralateral limb following unilateral sympathectomy probably then has some other basis.

The presence of B fibres in the sympathetic outflow to the limb in mammals has not hitherto been conclusively proven. Erlanger and Gasser[5] had shown that in the frog the sciatic B potentials must pass through the grey rami. On stimulating the grey rami in cats and dogs all the successful preparations gave C waves in the femoral nerve, but Erlanger goes on to say in a "relatively few . . . an elevation with the threshold and rate of conduction definitely within the B range" (10.5 m. per sec.) was also detected. However, if the recording electrodes were placed on branches of the "sciatic plexus" B waves could not be obtained. The existence of B as well as C potentials, amongst the responses, here shown to be autonomic by their disappearance after nicotine, is of considerable interest. The presence of the corresponding B fibres implies the possibility of control over effectors differing in function and distinct from those supplied by fibres of the C group. The number of B and C fibres contributed by each root would then determine the possible extent of its control over the various types of sympathetic responses. This is but one tentative interpretation. If the scarcity of B waves in the responses from the radial nerve, as compared with those from the ulnar and median, turns out to be an accurate picture one wonders whether it might be related significantly to a difference in anatomical distribution. The ulnar and median nerves supply the palmar surface of the hand, an area which sweats profusely under emotional stress. The cutaneous distribution of the radial nerve on the other hand is confined to the back of the arm and forearm and dorsum of the hand, where emotional sweating is negligible. May there not be some correlation between the autonomic B fibres in the ulnar and median and the sudomotor function of these nerves? The data are not extensive enough to answer the question with assurance. The significance of the finding that B waves form only a decidedly minor part of the sympathetic potentials in the monkey as compared to the cat awaits final interpretation of the function of autonomic B fibres.

SUMMARY

1. The sympathetic preganglionic outflow from the spinal cord to the limbs has been re-investigated by recording action potentials in the peripheral nerves following stimulation of ventral roots.

2. In the cat the outflow to the lower extremity extends from T11-L4, with the major contribution from T13-L13 (inclusive), whereas in the Rhesus monkey (*Macaca mulatta*) it extends from T12–L3, with the major contribution from L1–L3 (inclusive). Thus 7 spinal roots in the cat participate in the outflow to the lower limb, whereas only 4 roots contribute in the monkey.

3. The sympathetic preganglionic outflow to the upper extremity extends in the Rhesus monkey (*Macaca mulatta*) from T4–T8 (inclusive) with the major outflow from T5, T6, and T7. This outflow is also more restricted than that observed in the cat and dog by previous workers.

4. There is no definite difference between the extent of total outflows to the median, ulnar and radial nerves, nor between the outflows to the medial and lateral popliteal branches of the sciatic.

5. Variations in the fixation of the lumbo-sacral and brachial plexuses were not associated with any clear differences in the preganglionic outflows to the limbs.

6. Crossed pathways, between the lumbo-sacral sympathetic chains, of fibres destined for the opposite sciatic nerve were not demonstrated in either the cat or the monkey.

7. Large C waves were recorded in both "animals." B waves were recorded in the cat, but were only occasionally seen in the monkey.

8. Nicotine injected intravenously in suitable doses abolished both B and C waves, thus establishing their autonomic nature.

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RECOVERY OF RESPONSIVENESS IN MOTOR AND SENSORY FIBERS DURING THE RELATIVE REFRACTORY PERIOD

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IN THE course of experiments designed to show whether fatigability is different in sensory and motor nerve fibers, it appeared necessary to determine whether there were differences between the curves of recovery during the relative refractory state *without fatigue.*

METHOD

Twenty-five bullfrogs and 10 cats were used for the experiments. The bullfrogs were generally pithed and the 8th and 9th spinal roots cut at their entrance into the cord. The tibial and peroneal nerves were cut at the knee. In some cases the entire sciatic nerve with its spinal roots was excised and set up in a moist chamber; in others the nerves were left *in situ*. In 7 experiments recovery was observed also in the isolated roots. Most of the cats were spinal animals; a few were narcotized with dial. Their 6th and 7th lumbar roots were ligated and cut centrally, and here too the popliteal nerves were cut.

The conditioning and the testing shocks were delivered by two Harvard coils, with the secondaries in series. The primary circuits were opened by means of two keys on a Lucas pendulum, the circle of which was divided into quarter degrees. The speed of the pendulum, taken as constant for the small intervals used, was $1\frac{1}{4}$ degrees per msec. The limit of accuracy in setting the pendulum was about 0.04 msec. As we were interested chiefly in the recovery of responsiveness (height of spike) and not of excitability, we used strong testing stimuli, generally three or five times stronger than just maximal. In a few experiments in which we tested the same nerve with stimuli three, four and eight times maximal, there was almost no change in the shape of the curve. Thus we were assured that the curves obtained did not depend upon the *number* of fibers excited but represented the average height of the potentials in *all* the fibers at each interval. Choosing the right strength of conditioning stimulus for the sensory fibers occasionally offered difficulty. Sometimes the α wave of the second response at short intervals overlapped the β wave following the testing stimulus. Therefore, it was important that the β wave should have a constant height in order to make accurate measurement of the second α response possible. That is, the testing stimulus had to be strong enough to elicit a maximal β response. Otherwise at short intervals summation of the second stimulus with the first one might have excited β fibers that had not responded to the first stimulus alone, thus making the second α response appear higher than it actually was. Figure 1, a series of original records from a sensory root, is a good example of how necessary it was that the β fibers be stimulated maximally by the conditioning shock. On the other hand, if the conditioning stimulus was too strong there was danger of repetitive response of the α fibers. Sometimes in sensory roots of the cat (L6 and L7) there was a poor separation of the α and β spikes so that it was difficult to measure the height of the first. The pictures of double responses of sensory fibers were not always so easily interpreted as those in Fig. 3. Frequently if the recording electrodes were placed close to the cut end of the root in the cat, very small potentials were obtained; but the responses became normal when the electrodes were shifted a few millimeters peripherally. It was not determined whether recovery also was impaired near the cross-section of the roots, but this seems highly probable. Hence in placing the electrodes on the roots too near their cut ends, there was a source of error hard to avoid. Therefore experiments on roots giving strong action potentials seemed far more reliable than those on roots with poor potentials. Generally the stimuli were applied either at the central or at the peripheral end of the preparation, the recording electrodes being placed at the opposite end.

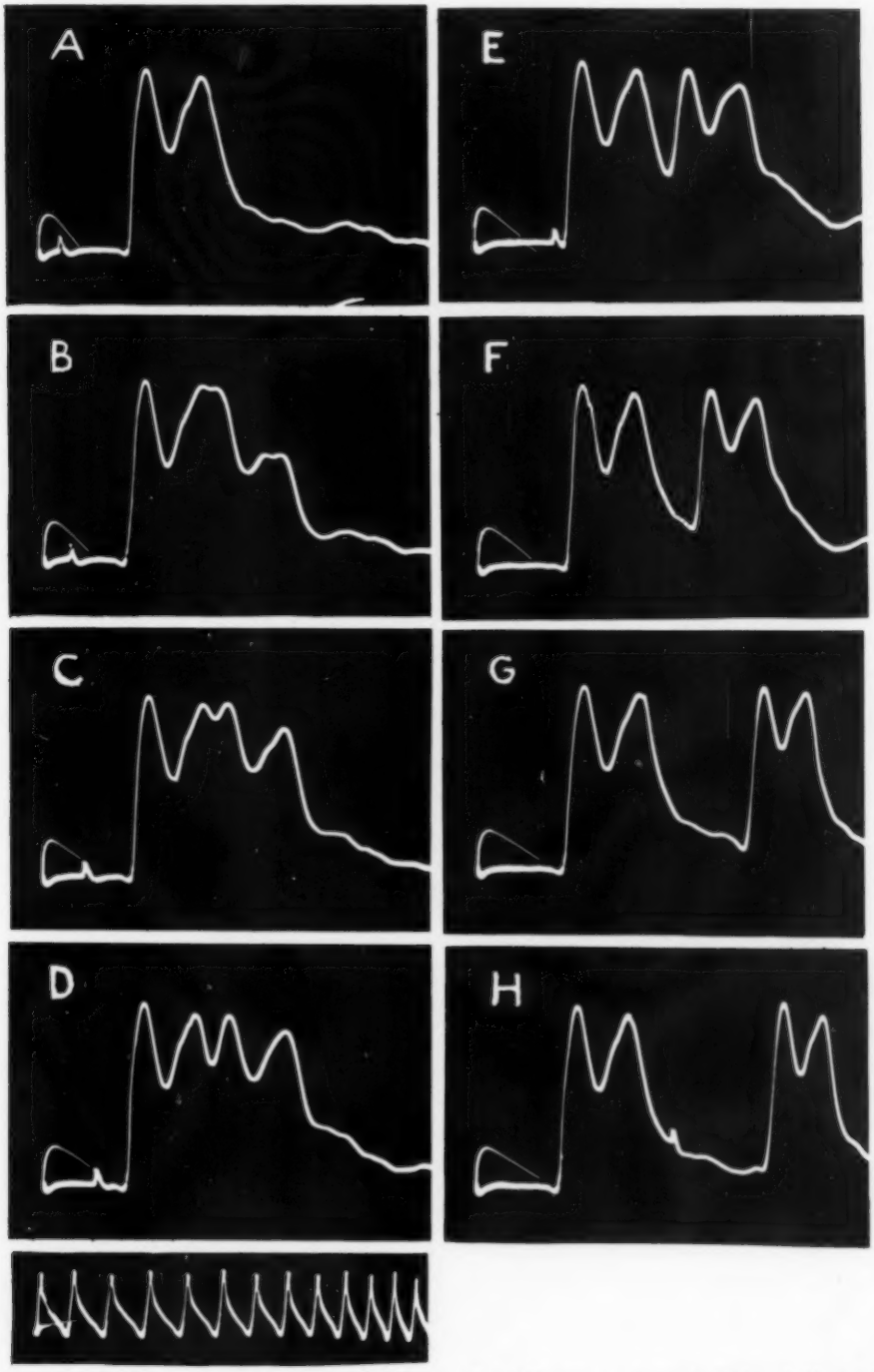

FIG. 1. Action potentials recorded from the 9th sensory root. Stimulation of the sciatic nerve *in situ*. Time intervals between conditioning and testing stimuli in successive pictures: 1.1, 1.3, 1.7, 2.1, 2.7, 3.7, 5.1 and 6.3 msec. Time: milliseconds. (Bullfrog 29; 7-20-40, Temp. 27°C.)

The action potentials were led through a Grass condenser-coupled amplifier and registered on a cathode ray oscillograph adjusted for a single sweep controlled by the Lucas pendulum to start simultaneously with the conditioning shock. For both stimulation and recording Ag electrodes were used.

Results

Frog experiments. The shortest absolute refractory state observed lay between 0.6 and 0.8 msec. (Temp. 25 to 28°C.). In the nerves *in situ* these abnormally long periods probably were due to the inevitable impairment of

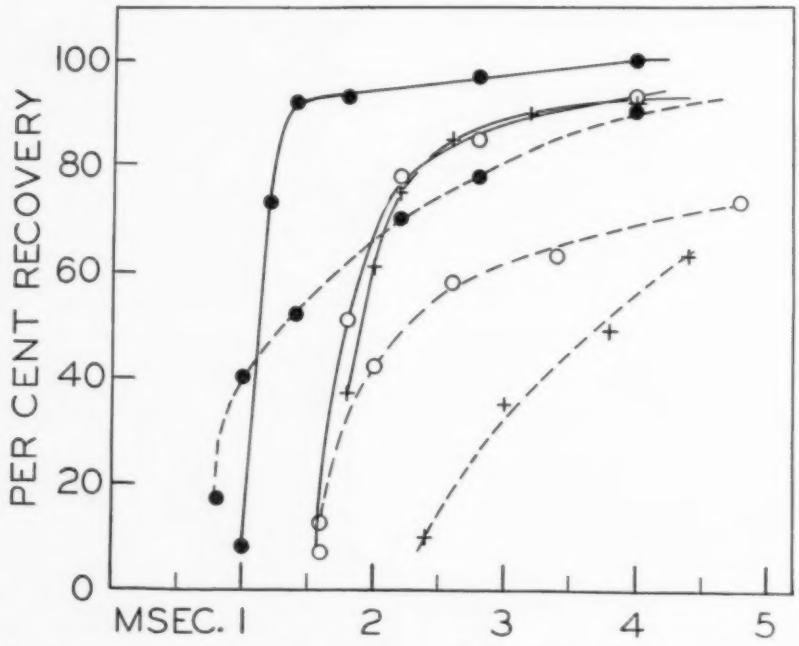

Fig. 2. Recovery of height of α potentials during the relative refractory period in motor (solid lines) and sensory (broken lines) fibers in three bullfrog experiments. Dots: recorded from the roots, nerve *in situ* (Bullfrog 22; 5-28-40). Circles: recorded from the roots, nerve *in situ;* the sympathetic rami to the lumbar plexus had been cut (Bullfrog 18; 5-7-40). Crosses: recorded from sciatic trunk, roots stimulated, excised nerve (Bullfrog 15; 4-27-40). Abscissae: interval between conditioning and testing shocks. Ordinates: height of conditioned response in per cent of height of first response.

circulation arising from pithing and the preparation of the roots. In some cases the absolute refractory period was even as long as 2 msec. Often, but not invariably, the dorsal roots showed the longer periods (cf. Fig. 2).

The curves showing recovery of responsiveness in motor fibers varied from frog to frog. Most of them showed a steep initial rise, attaining about 80 to 95 per cent recovery within 0.5 msec. after the end of the absolute refractory period. This was followed by a slow increase to 100 per cent, the curves in general being knee-shaped (see Fig. 2, motor curve indicated by dots). In some cases this knee did not appear so sharp. If the experimental

points had been closer together these curves might have approached the others in form (Fig. 2, motor curve indicated by circles). In a few cases where the roots had been stretched, complete recovery was much slower; the initial rise of the curve showed typical steepness, but the knee occurred when recovery was not so far advanced as usual (in one case only 50 per cent).

Recovery of responsiveness in the sensory fibers was always much slower and the knee-shape so often found in motor curves was absent. Ninety per cent recovery was obtained on an average within 0.8 msec. after the absolute re-

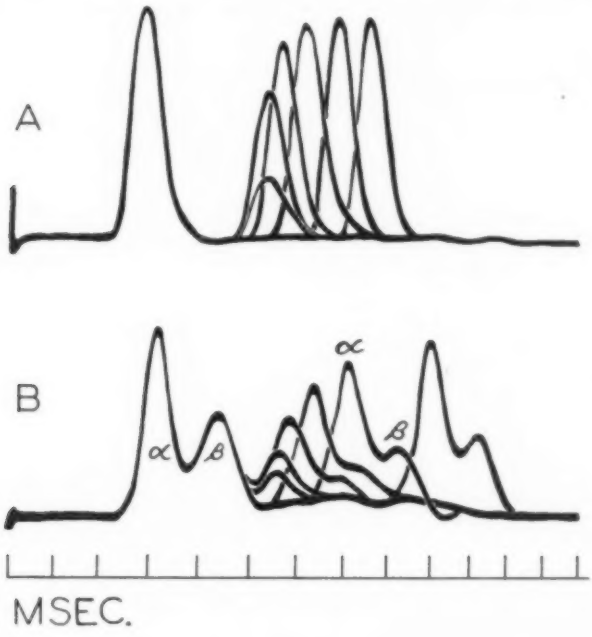

FIG. 3. Action potentials of motor fibers (A) and sensory fibers (B) recorded from the sciatic nerve. The 8th and 9th roots together were stimulated with two maximal stimuli, the testing stimulus following the conditioning one at intervals of 1 4, 1.6, 2.0, 2.6, 3.6, 4.4 (curves A and B) and of 5.2 (curve B) msec. Nerve and roots in moist chamber. Successive pictures have been superimposed by projection so that the first responses are coincident. (Bullfrog 10; 5-5-40.)

fractory period in the motor curves and within 4 msec. in the sensory. A survey of motor and sensory curves of all the frogs used shows that in spite of the great individual differences there was a clear segregation of sensory curves from motor. The slowest motor curves were approximately coincident with the fastest sensory ones. Yet there generally was a certain relation between the rate of recovery in these two sets of fibers, a relatively quick motor recovery being associated with a relatively less slow recovery in the sensory fibers (cf. Fig. 2). Among about 40 pairs of motor and sensory roots, only two were found having identical curves; in no case did the sensory root recover more quickly than the motor. Figure 3 further illustrates this marked

functional difference between motor and sensory α fibers. Although accurate measurements of the heights of the β waves could not be made, the curves in *B* (Fig. 3) indicate that recovery in these fibers was still slower than in the sensory α fibers.

In many cases repeated observations were made on the same preparation. When there was evidence of deterioration of the nerve, such as drying, successive curves were found to become slower (cf. Fig. 4). However, later curves taken on nerves which were apparently still in good condition showed a

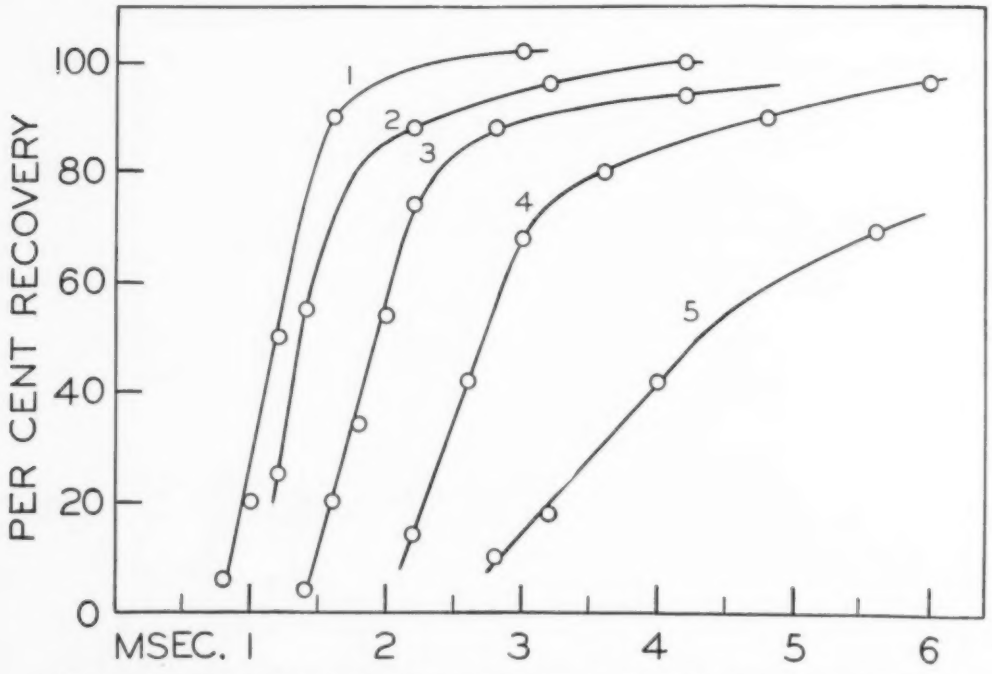

FIG. 4. Effect of gradual drying-out on recovery of height of spike during relative refractory state. Pithed leopard frog in moist chamber, recording from tibial nerve *in situ*. Double stimuli applied to sciatic high in the hip. Curves 1 to 5 taken at 2:42, 3:05, 3:45, 4:08 and 4:22. At 4:25 nerve found very dry. (5-22-40.)

tendency to become faster. These observations confirm similar findings of Graham (1934). In Fig. 6 a curve taken from a sensory root 29 hours after excision showed that recovery was faster than on the previous day.

Measurements on recovery of conduction velocity (calculated from the time interval between the start of the testing stimulus and the foot of the recorded spike) were made on nerves of 8 bullfrogs. This method was used in spite of the recognized inaccuracy involved (Graham and Lorente de Nó, 1938). It is remarkable that no constant difference between recovery of conduction velocity in motor and in sensory fibers was found. The motor and sensory curves were either identical (cf. Fig. 5) or showed only slight variations in either direction. At the start of the relative refractory period,

velocity was generally reduced to about 60 per cent. The greatest reduction seen was to 55 per cent, at an interval of 1 msec. Recovery of velocity was faster than that of size of response in the sensory fibers but slower than recovery of responsiveness in the motor (cf. Fig. 5).

To determine whether slowness of recovery of responsiveness was an inherent characteristic of the dorsal root fibers, recovery curves were taken for the excised 9th sensory and motor roots of 6 bullfrogs, the spinal ganglia having been cut away. Unexpectedly, these curves were found to be similar

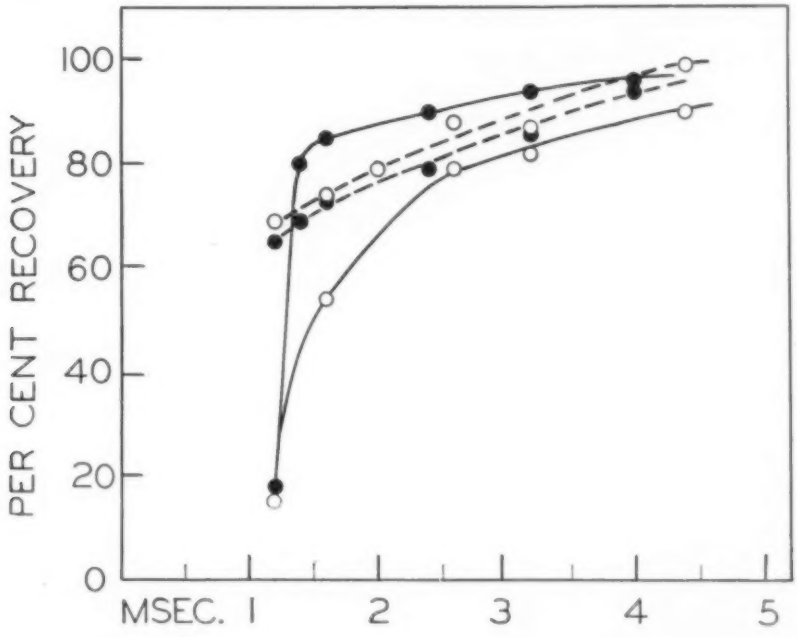

FIG. 5. Recovery of responsiveness (solid lines) and conduction velocity (broken lines) in sensory (circles) and motor (dots) fibers, recorded from the sciatic trunk. Excised nerve in moist chamber. Abscissae: interval between conditioning and testing shocks. Ordinates: height of conditioned response in per cent of height of first response, and conduction velocity of conditioned impulse in per cent of velocity of first impulse. (Bullfrog 15; 4-27-40.)

and in some cases even identical. Recovery of responsiveness of sensory fibers was much faster in the cut root than when these fibers were tested in either direction as part of the root-nerve preparation. Figure 6 illustrates this behavior. Later, stimulating the 9th spinal nerve 2 to 3 mm. peripheral to the spinal ganglion and recording from the central end of the dorsal root, we found the typical slow recovery curve, whereas by shifting the stimulating electrodes to a point the same distance central to the ganglion we obtained the quick curve (two experiments). Figures 4 and 6 seem to show a recovery of spike height to more than 100 per cent. As no supernormal phase ever has been observed in recovery of responsiveness (Graham, 1934) this

overshooting may be due to error in method. Often recovery curves of cut ventral roots showed no difference from those of the root-nerve preparations. However, when the latter had the sharp knee-shape, the curves of the same roots when isolated were somewhat slower (rounded off).

As sensory fibers in toads contain only $\frac{1}{6}$ of the acetylcholine (ACh) concentration found in motor fibers (Chang, Hsieh, Lee, Li, and Lim, 1939) it seemed interesting to determine whether ACh has any influence on the re-

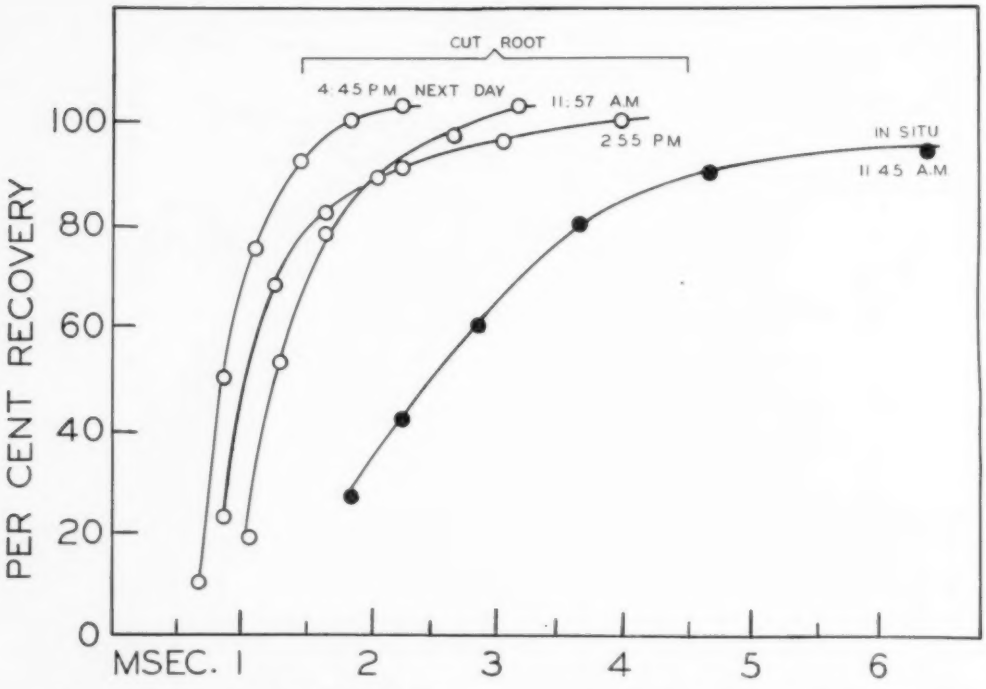

FIG. 6. Recovery of height of spike in a dorsal root during relative refractory period. Dots: stimulating electrodes on sciatic nerve *in situ*. Circles: experiments on the same root excised without the ganglion. (Bullfrog 31; 7-20-40.)

covery of responsiveness. Sciatic nerves of some leopard frogs and spinal roots of 6 bullfrogs were excised. One of each pair was put into Ringer's solution; the other for $\frac{1}{2}$ to 1 hour into a solution of eserine sulfate 1:50,000 and afterwards for 1 hour or more into ACh 1:25,000 to 1:100,000. When these nerves were tested with double stimuli, no characteristic difference between recovery curves of Ringer and of ACh nerves could be seen.

Cat experiments. The characteristic difference observed between recovery of responsiveness in motor and in sensory fibers in the bullfrog did not appear in the cat. In some cases recovery in both roots was equal, in others it was quicker either in the motor or in the sensory (cf. Fig. 7). Although the shapes of the curves varied remarkably, the knee-shape, characteristic of the motor fibers in the bullfrog, was seldom seen (cf. curves indicated with circles in Fig. 7). In general, recovery in these cat experiments was markedly slower

than in the bullfrog *motor* fibers; in fact the cat curves were very similar to the curves of the *sensory* fibers in the bullfrog. In a few experiments on cut roots recovery was found to be quicker than in the root-nerve preparation; in others it was about the same. The number of experiments was too small to give conclusive results. The relatively low temperature (about 31°C.) in the moist chamber into which the dorsal wound had been transformed may account for the relative slowness of the cat curves.

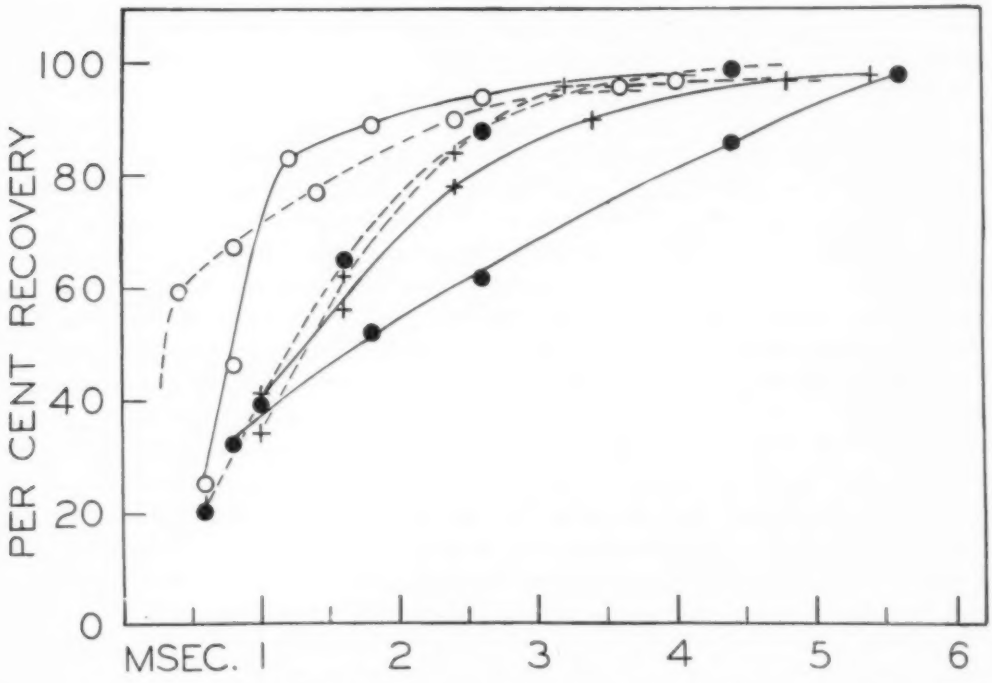

FIG. 7. Recovery of height of α potentials during the relative refractory period in ventral (solid lines) and dorsal (broken lines) roots in three pairs of cat nerves. Stimulating sciatic nerve *in situ*; recording from lumbar roots. Circles: Cat 2, L7, 5-18-40; crosses: Cat 9, L6; dots: Cat 9, L7, 7-15-40.

The absolute refractory period on the whole was shorter than in the bullfrog experiments. Often a second response was seen at an interval of 0.6 msec. and in a few cases even at 0.4 msec.

In 5 experiments recovery of conduction velocity was measured by the method described in the former section. These curves closely paralleled the curves of recovery of height. The greatest reduction in velocity observed was to 40 per cent at an interval of 0.6 msec.

In cat fibers also ACh was found to have no observable effect upon recovery of responsiveness.

DISCUSSION

The outstanding result of these experiments is the characteristic difference between the curves of recovery of responsiveness in motor and in

sensory fibers in root-nerve preparations of the bullfrog. As the experiments with cut roots demonstrate that the slow recovery is not an inherent quality of the sensory fibers, the question arises as to the cause of the observed difference. Since this same difference was found in experiments in which the stimuli were applied either to the root or to the peripheral end of the nerve, it cannot be due to any influence set up in the nerve trunk. It appears that the *spinal ganglion* must be the source. That the difference arises only when the impulse passes through the ganglion, its presence alone not being sufficient, is concluded from an experiment in which the root had been stimulated centrally from the ganglion before and after cutting the ganglion away, the same fast curve being obtained in both cases from the root.

The phenomenon is independent of the blood supply to the ganglion, since it was observed in root-nerve preparations both excised and *in situ*.

The simplest explanation of the phenomenon would be the assumption of a temporal dispersion of the α spikes during the passage through the ganglion, reducing the height of the spike by broadening its base. Erlanger and Blair (1938) studying single impulses found it not "possible to substantiate a lag in the propagation through the ganglion." It still seems possible, however, that a *conditioned* impulse travelling more slowly might be retarded. If this retardation were different for different fibers, it might account for the observed effect. The question whether or not this is the case might be checked by comparing the areas under the conditioned spikes at given intervals in experiments in which the root spikes were recorded when stimulation was applied both central and peripheral to the ganglion. Such a comparison is possible only if the "preganglionic" stimulation is applied fairly close to the ganglion; otherwise, a long conduction path allows the α and β waves of the first impulse to separate, making it impossible to see the actual initial rise of the conditioned α wave (cf. Fig. 1). With preganglionic stimuli close to the ganglion, the rise of the conditioned response is clean. If the reduction in height of the spike after passing the ganglion is purely a matter of retardation, the presence of the β wave in the conditioned response should not interfere with the comparison. This comparison was made for three pairs of spikes. In each case the area under the spike that had passed the ganglion was found to be decisively smaller than under the other. The fact that this characteristic difference between motor and sensory roots after stimulation of the mixed nerve does not appear in the cat preparation is another point against the idea of temporal dispersion.

Thus, in spite of the fact that the explanation by temporal dispersion would be by far the simplest, it does not seem acceptable. Even if one might assume decremental conduction in the region of the ganglion, one would expect the impulse to return to normal as soon as it had passed the ganglion.[1]

[1] Dr. R. W. Gerard has suggested to us the possibility that slow recovery of excitability in the ganglion might cause complete blocking of impulses in some of the fibers with a consequent reduction in the total response recorded beyond the ganglion. Our results may well be interpreted on this basis.

It appears necessary to assume that the passage of the impulse through the ganglion really modifies the responsiveness of the fibers beyond the ganglion during the relative refractory state by causing the spread of an influence along the fibers. Such an influence might be either electrotonic or chemical. In the latter case the chemical process of which the spike potential is an indicator would be modified during and after passage through the ganglion. Since in a series of side experiments we could detect no influence of ACh on recovery of responsiveness in isolated roots, it does not seem probable that this substance is the cause of the phenomenon.

The question as to how far the presence of the ganglion cell influences the nerve fiber arising from it has been frequently discussed ever since Fröhlich and Loewi (1908) postulated in a cephalopod the "feeding" of a nerve by its ganglion with a substance necessary for nerve excitability. On the basis of our present knowledge it is not profitable to discuss this question further.

In the course of the experiments described in this paper, recovery of excitability was studied only occasionally, but our experiments confirmed Graham and Lorente de Nó's (1938) results showing that recovery of conduction velocity occurs more promptly than that of excitability and that there are no late changes in velocity and in responsiveness corresponding to the supernormal and subnormal periods of excitability. The fact that conduction velocity recovers at the same rate in sensory and in motor fibers, in spite of the marked difference in recovery of responsiveness, may be of interest for the theory of propagation of the nervous impulse. Erlanger and Blair (1938) found that the sensory fibers in the bullfrog's sciatic are much more excitable than the motor and yet they both conduct at about the same velocity. They suggest that the "tendency the high excitability must exert towards hurrying propagation might be counterbalanced by the increased number of restimulations needed per unit of distance traversed" (shorter segments between the nodes of Ranvier). If conduction depends on restimulation by eddy currents reaching threshold strength for the adjoining segment of the fiber, conduction velocity must depend also on the time elapsing between the start of the local potential and the moment when it reaches threshold strength for the next segment. This time being longer in potentials of low voltage, recovery of conduction velocity ought to be slower in sensory fibers after passage through the ganglion than in motor fibers. The fact that this is not the case may be due to a counterbalance exerted by the higher excitability of the sensory fibers. The absolute magnitude of motor and sensory action potentials was not measured in our experiments. Yet the fact that when the same amplification was used the potentials of motor fibers were always much greater than those of sensory α fibers might indicate that motor fiber potentials are of higher voltage than sensory ones. This is in accord with Erlanger and Blair's (1938) observation that in the bullfrog the demarcation potential of the sensory root is lower, by roughly a third, than that of the motor root. A relatively lower voltage in sensory fiber potentials

should also be kept in mind as a possible counterbalance to the influence higher excitability exerts on conduction velocity.

In 1937 Gasser discussed whether one might suppose that the relative refractory period and the subnormal period which occurs during the positive after-potential are one continuous event into which is interpolated a supernormal period associated with the negative after-potential. Gasser at that time did not accept this point of view, because it was held that, whereas the spike remained full sized during the subnormal period, it was *undersized* during the relative refractory period. In the following year it was shown by Graham and Lorente de Nó that recovery of responsiveness and of excitability during the relative refractory period occur at quite different rates, responsiveness being fully recovered at a time at which excitability still is much reduced. In many of our experiments on bullfrog and leopard frog α fibers the correctness of this statement has been fully confirmed, and Grundfest (1939) found the same to be true for β fibers. According to these results Gasser's suggestion is no longer to be rejected (as it was by himself in 1937). No fact is known incompatible with the view that the subnormal period is a late continuation of the relative refractory period but separated from it by a phase of supernormal excitability.

Summary

Recovery of responsiveness (height of spike) and of conduction velocity in motor and sensory fibers during the relative refractory state was studied in bullfrogs and cats. A Lucas pendulum was used for timing the stimuli and a cathode ray oscillograph for recording.

In bullfrogs recovery of responsiveness in the sensory fibers including the spinal ganglion was always much slower than in the motor fibers. The sensory and motor curves attained 90 per cent recovery within about 0.8 and 4.0 msec. respectively after the end of absolute refractoriness. In dorsal roots *without* ganglia, however, responsiveness recovered at the same rate as in ventral roots.

The passage of the impulse through the ganglion seems to modify the responsiveness of the fibers beyond the ganglion.

In cats recovery of responsiveness was slower in general (average temp. in moist chamber 31°C.) and no influence of the spinal ganglion could be observed.

In both bullfrogs and cats conduction velocity recovered at the same rate in sensory fibers including the spinal ganglion and in motor fibers.

Acetylcholine was found to have no observable effect upon recovery of responsiveness.

It is suggested that the subnormal period is a late continuation of the relative refractory period (cf. Gasser, 1937).

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TECHNIQUE AND EVALUATION OF THE ELECTROENCEPHALOGRAM*

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INTRODUCTION

EVER SINCE Berger in 1929 first described the human electroencephalogram (EEG), investigators have attempted to describe and interpret these records. Our experience is based on 5 years of standardized recording of more than 1100 individuals, both normal and abnormal, and it now seems worth while to set forth our own attempts at a systematic evaluation.

This paper deals with four objectives: (i) A description of standardized technique, which is the basis of other papers already published and in preparation. (ii) A description and evaluation of some of the previous and current methods of measurement. (iii) A classification of fundamental types of EEG patterns useful for description and correlation. (iv) A system of evaluation as to degree of normality and abnormality.

Selection of individuals. The individuals, 15 or more years of age, whose EEG's have been recorded, have been classified with respect to their "normality." We fully realize that there is a large subjective factor which cannot be excluded when evaluating human beings and their behavior. Nevertheless a person's medical history and his behavior under different conditions and in different environments, judged by several individuals who know the person, seems to us to constitute the soundest and most practical basis for classification. The definitions of the various categories are as follows:

1. *Selected normal.* On these individuals we have extensive and reliable medical and social history. Their medical history is within normal limits and reveals only the ordinary childhood diseases without unusual sequelae. There is no history of even one convulsion, regardless of cause. There have been no psychiatric problems necessitating care, nor have there been questionable relationships with others. Their behavior has been normal and wholesome at home, at school, at work and at play.

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* Although the editorial policy of the *Journal* has been never to accept papers dealing solely with technique, a unique exception has been made in this case. The Editors have desired to assist in making this technique available as soon as possible since its application at the moment to problems of aviation medicine seems pressing. ED.

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2. *Presumably normal.* Information on this group is less complete, but, as far as it goes, indicates that the individuals are normal. The group includes many college and medical students whose school, social and home life is known to some extent. The group thus differs from the usual so-called "control" group.

3. *Unknown.* The group includes casual visitors, friends of friends, employees or students not well known to us.

4. *Abnormal. A. Outside hospital.* Persons belonging to this group are those who have needed psychiatric attention and those whose inability to adapt to ordinary circumstances is obvious to their friends or associates. Under this heading are epileptics or people whose history reveals one or more convulsions, even though they are apparently normal.

B. Patients in mental hospital. This group includes mostly patients in mental hospitals [McLean Hospital (private patients, unselected)]. Aside from these, there are a few cases from general hospitals whose condition involves psychiatric or neurological problems.

Procedure

In the first year many experiments were performed in attempts to modify the EEG. The results showed that it was important that the subject be at ease and free from apprehension in relation not only to the procedure, but also to the person who records him. It was found that a light-proof or sound-proof room is not conducive to putting the person at his ease. If the eyes are open, it is not only light which modifies or reduces some of the rhythms of the EEG, but the fluctuation of attention and the adjustment of "psychological set" (Davis, P. A., 1939; Davis, H. and Davis, P. A., 1939) which tend to alter the stability of the record. Our standard procedure, which fulfills the optimum conditions for stability, requires that the person be comfortably relaxed but thoroughly awake, with his eyes closed, on a bed facing away from the source of light in a diffusely lighted room. The subject should be clearly in view at all times if it is not possible for him to be in the room with the recorder. It is essential that conversation or whispering between recorder, another doctor or nurses be strictly avoided during the procedure so that recorder and subject can maintain a friendly rapport throughout.[1]

Apparatus. The ink-writing oscillograph with its amplifiers and broad-band filters, built by Mr. Albert M. Grass for the study of the EEG, has become standardized for routine recording since we began our studies. The speed of the tape is 3 cm. per sec. The standard sensitivity is 1 cm. for 100 μV. The frequency characteristic of the recording system is

[1] Persons being recorded under standard conditions should be known to be free of drugs, even as common a one as aspirin, for several days before recording. For instance, one of our patients showed an elevated blood-bromide level for 3 weeks after cessation of medication with sodium bromide and the EEG became normal only after the blood-bromide concentration had fallen to the normal range. And it is not only the drug but the fact that the condition of the person is such that any medication is required that implies that he is not in perfectly normal condition. Throughout this paper all measurement data on both normal and abnormal people are based on subjects free of medication and recorded under standard conditions.

flat from 3 to 65 cycles. The upper limit is often deliberately reduced by a "muscle filter," which is built into the power amplifier, to 50 cycles so that extraneous electrical disturbances and muscle potentials are reduced to a minimum. A time-constant of the system of 0.15 sec.[2] is found satisfactory for standard records.

Tuned electrical filters have been built so that they can be included or excluded in the circuit as desired. The frequency-bands of these filters are broad,[3] and overlap considerably. The peaks of the frequency-bands have been arranged fairly close together and extend from 3 to 35 cycles. Thus a 10-cycle filter has a broad peak at 10 cycles. It will pass 9 and 8 and even 7 cycles on one side, and 11, 12, and 13 cycles on the other side, although the amplitudes of the waves will be somewhat less. Up to and through 1939, the filters Mr. Grass has built and which we have used are tuned to 3, 5, 7, 10, 14, 17, 23, 28, and 35 cycles.

Amplification is increased when the filters are employed, so that waves at the frequency to which the filter is tuned appear at approximately double the amplitude that they show

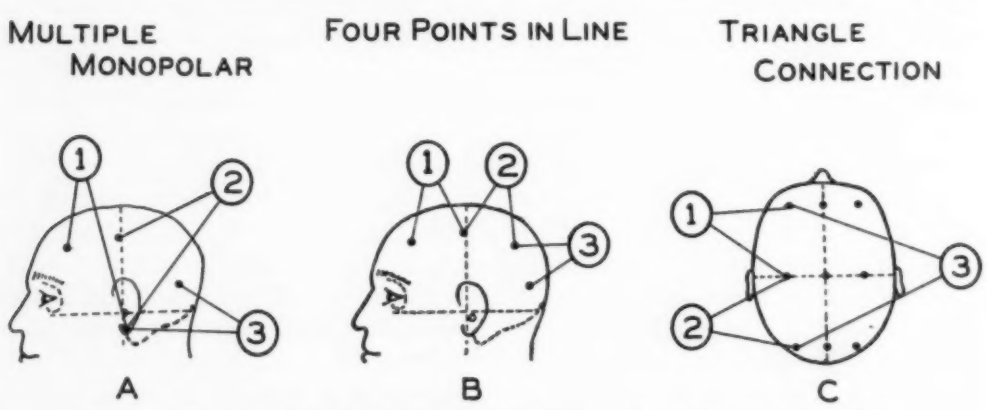

FIG. 1. Placements on head representing different techniques of recording. The numbers represent the amplifiers.

in the standard unfiltered record. When the filters are switched into the circuit, standard amplification for them is obtained by decreasing the attenuation four steps on the Grass amplifiers.

At present we are using a 3-pen recorder, with broad-band filters and perfectly matched amplifiers. The amplifiers are provided with balanced push-pull input stages which are not directly connected to ground. Therefore the three systems are non-interfering and completely independent of one another.

Multiple "monopolar" recording. Unless otherwise specified we shall deal in this paper with multiple monopolar records. We have regularly used the lobes of the ear as our reference point, as shown in Fig. 1A. Specially constructed ear-clip electrodes are very conveniently applied. Control experiments show that the ear is electrically much less active than points on the cranium. The mastoid process has been found to be unsatisfactory because of its proximity to the temporal region.

[2] When a constant potential difference is applied to the input leads of a condenser-coupled amplifier system the recording pen registers a quick deflection followed by a relatively slow return to the base-line. The "half-time constant" of the system is the time required for the pen to return halfway. The "time-constant," more generally employed by electrical engineers, is the time required for it to return to $1/e = 1/2.718 = 0.368$ of its initial deflection. The longer the time-constant the lower is the frequency of an alternating current that will be recorded without attenuation.

[3] The breadth of the band is conveniently defined in terms of the frequency whose voltage is attenuated to one-half of the voltage that is delivered at the resonant frequency at the center of the band. For our present filters the ratio of frequency for 50-per-cent attenuation to the resonant frequency is 1.55, *i.e.*, the filter tuned to 10.1 cycles attenuates by 50 per cent the waves at 15.7 or 6.4 cycles. The breadth of band is the same for all

Table 1

First, unfiltered at standard, then at increased sensitivity.
Second, all filters at their standard sensitivity.

Nine-point routine
Multiple monopolar recording

Simultaneous recording of *one* area on the *two* sides of the head

	A	*B*	*C*
Line 1	Left occipital	Left precentral	Left frontal
Line 2	Right occipital	Right precentral	Right frontal
Line 3	Mid occipital	Mid precentral	Mid frontal

Simultaneous recording of *three* areas on *each* side of the head

	D (*left side*)	*E* (*right side*)
Line 1	Left frontal	Right frontal
Line 2	Left precentral	Right precentral
Line 3	Left occipital	Right occipital

Bipolar record by "triangle" connection, if indicated

Line 1	Left frontal to left precentral	Right frontal to right precentral
Line 2	Left precentral to left occiput	Right precentral to right occiput
Line 3	Left occiput to left frontal	Right occiput to right frontal

Bipolar record by four points in line

Line 1	Left frontal to left precentral	Right frontal to right precentral
Line 2	Left precentral to left parietal	Right precentral to right parietal
Line 3	Left parietal to left occiput	Right parietal to right occiput

frequencies except the lowest which is very broadly tuned to 2.8 cycles with a band-width ratio of 2.5. This "delta filter" is very useful in dealing with irregular slow waves.

Multiple "bipolar" recording. This method employs two "active" electrodes on the cranium and no reference electrode. Figure 1B shows the "four-points-in-line" arrangement, which is one form of bipolar connection. It will be observed that 2 amplifiers have an electrode in common. For a description of the use of this type of recording for localization of tumors see Williams and Gibbs (1938).[4]

"*Triangle connections*" shown in Fig. 1C may or may not involve the reference point as one point in a closed triangle. The principle is similar to that of the four-points-in-line in that each amplifier records the activity from two points on the head. By comparing the activity coming from each pair of electrodes, one may localize the source of specific or unusual activity (Jasper and Hawke, 1938). If the points are close to one another the amplification may have to be increased in order to bring out the detail. Sometimes the activity under one electrode cancels out the activity under the other electrode (see also Kornmüller and Schaeder, 1938). It will be seen that this four-points-in-line differs from the triangle connection, not in principle, but by using the fourth point instead of returning to the first point in the triangle.

Electrode placements. In 1935–36 our electrode placements were on the mid-line, in the occipital, vertex, and frontal areas. The occipital placement is approximately 2 cm.

[4] Dr. Goodwin of the Banting Institute in Toronto has pointed out (personal communication) that in bipolar recording an electrode over a tumor may act as a reference electrode. The resultant record would be like a monopolar record because tumors are known to be electrically inactive.

above the inion. The vertex is the point at which the frontal plane through the auditory meatus intersects the mid-line. The frontal placement is a point on the forehead in the mid-line just below the usual hair-line. More recently, with the 3-pen recorder, lateral placements 5 or 6 cm. on both sides of the mid-line have been added (cf. Fig. 1A) and for a more complete study a routine of 16-point placements divides the surface area of the head by spacing the electrodes at equal distances from one another, starting approximately 2 cm. on either side of the mid-line on the frontal, precentral, parietal and occipital areas. The resistances of the electrodes (solder pellets and Sanborn electrocardiogram paste) pasted with collodion on the scalp, are kept under 10,000 ohms as routine. High resistance may cut down the amplification and pick up extraneous artefacts.

Routine. With a tape-speed of 3 cm. per sec. and a sensitivity of 1 cm. for 100 μV., a routine record is run for 20 min. as a minimum, up to 1 hr. as a maximum. First, several minutes of unfiltered record from one or more areas are taken. A filtered record is then taken at the increased amplification. During the unfiltered record and again during the 10-cycle record, the person is asked to open his eyes for 4 to 5 sec. and then close them again. This is done in order to bring out the modification of the alpha rhythm (Jasper, 1936). Next, an unfiltered record is always taken at increased amplification for detailed analysis.

Our most satisfactory routine for a 3-channel recorder is shown in Table 1.

If, from observation of the routine monopolar record, there appears to be anomalous electrical activity, multiple bipolar recording is employed to localize further the unusual activity coming from one or another part of the brain, which may necessitate the application of more electrodes to other areas.

Measurements

Once individuals have been classified as normal, presumably normal, or abnormal and their EEG's obtained by standardized procedure, the problem is then to develop some method of evaluation which will differentiate between the EEG's of the normal and the abnormal group. A first glance at a collection of EEG's reveals in all records an interplay of waves and a fluctuation of voltages. Since many of the waves seen in the EEG's form groups of countable frequencies, we first selected frequencies for study and measurement. In 1935 and 1936 we made a detailed study of the EEG's of our first 50 subjects. At that time we had no filters and consequently counted frequencies wherever a half-second of time yielded at least 3 equally spaced waves, all of them at least 10 μV. in amplitude. For each mid-line area 100 counts were made on sections of records where the eyes were closed, and we confirmed Berger's (1929) observation that the most common frequency was approximately 10 cycles. The frequency-distribution curve showed a blunt peak at 10, which fell off at $8\frac{1}{2}$ to 9 cycles on one side and at 11 to 12 cycles on the other side. The next peak in the distribution curve was much lower and was in a less well-defined range from about 14 to 20 cycles. This curve tapered off more gradually on both ends.

Alpha rhythm. We regard as "alpha rhythm" only those frequencies near

10 cycles which are characteristically suppressed when the eyes are opened and closed under standard conditions (Davis, H. and Davis, P. A., 1936). The momentary speed-up of the alpha rhythm by as much as 1 or 2 cycles following closing of the eyes is a characteristic modification pointed out by Jasper (1936). The *normal* alpha range is from approximately $8\frac{1}{2}$ to 12 cycles (which does not include the speed-up of an alpha following "eyes closed") and we believe represents the activity of a particular physiological mechanism especially susceptible to modification by internal conditions.

If the physiological activity of a normal person is depressed, as it appears to be when one becomes drowsy, the alpha activity may be altered accordingly. For instance, if one is very sleepy the alpha activity gradually disappears. If a subject is asked to open his eyes at this stage, the alpha activity reappears when he *opens* his eyes and disappears again when he closes them once more and can relapse to his former state. There are all gradations between this state and the alert state. The alpha waves may become irregular instead of reduced when eyes are open, but this is an indication of a state wherein the alertness is decreasing. The alpha activity increases when the eyes are closed in an intermediate optimum state which lies between the alert and the drowsy state. It represents a definite transitory level of physiological activity.

In our series of normal adult records, the alpha activity, modified as just stated, does not include frequencies below $8\frac{1}{2}$ or above 12 cycles. There have been a few exceptional cases in the "presumably normal" group with alpha frequencies of 13 cycles. In our series of records from *abnormal* individuals, there are a number with alpha activity including frequencies as low as, or even lower than, 8 cycles and as high as 14 cycles. In some of these records, frequencies of 16, 18 or even 22 cycles may follow closing of the eyes. This is not the accelerated alpha activity, but an abnormal response. With abnormal individuals, particularly those in whose EEG's dysrhythmic qualities are observed, the physiological mechanism responsible for the alpha activity is apparently influenced in a wide variety of ways. The alpha range is not clean cut and it is difficult to define clearly what the alpha activity really is in such a person. For instance, there may be a large amount of $7\frac{1}{2}$ to 8 cycle activity alone, or it may merge with 10-cycle activity, both responding like the alpha rhythm. If the frequencies are mixed, and the alpha frequency is to be defined, the speed-up on "eyes closed" should be carefully noted, in order to determine which is the alpha rhythm. Simultaneous recording through 3 filters tuned to 14, 10, and 7 cycles is invaluable for such a determination. If a record is completely 6 or 8 cycle (Fig. 5, sec. 2) and there is no 10-cycle activity, it *may* be characteristic for an abnormal person or for his condition at the time of recording, as, for instance, in certain conditions of impaired consciousness, or it may be a 10-cycle alpha slowed by drugs. What is significant is that the underlying physiological mechanism has been modified or is abnormal.

It will be noted that our use of the term "alpha" is interpreted from the

point of view of physiological mechanisms. It is these activities which we are attempting to measure. In other laboratories "alpha" is not so specifically defined (*e.g.*, Harvey, 1939). Furthermore, it remains an interesting problem whether the 10-cycle frequency seen in rare instances in a certain stage of deep sleep, and also the 10-cycle or slightly slower frequency seen in the precentral area and not always clearly responsive to opening and closing of the eyes (Jasper and Andrews, 1938) are the same physiologically as the alpha rhythm seen in the occipital area. Until this problem has been worked out, some apparent contradiction will remain when workers in the field discuss the alpha rhythm, its behavior, and significance.

In all our studies of the EEG, the pattern of the occipital area in normal people appears to be the most stable, and, if an alpha frequency is seen in the EEG, the normal occipital record shows it more than any other area. As one moves from the occiput forward toward the frontal area the percentage of time the alpha frequency is present decreases (but cf. also Rubin, 1938).[5] The parietal region is a transition area from occipital to temporal and motor regions. The temporal area is likely to show less alpha activity than the motor area. The EEG at the vertex is variable. The frontal EEG is often distorted by artefacts such as eye movements and muscle potentials. For these reasons, the occipital EEG was chosen as the basis for measurement of alpha activity. The definition of types of EEG pattern, to be described below, is also based primarily on the occipital record.

We do not agree with Jung's (1939) conclusion that in normal persons practically no alpha waves are generated in the anterior half of the brain. Jung explains the appearance of alpha waves in "monopolar" frontal and precentral records as due to changes of potential at the "reference" *ear* lead, induced by the activity of an alpha focus low in the occipital lobe. The characteristic equality in phase and voltage of frontal alpha waves in two hemispheres (in contrast to the independence of alpha activity in the two occipital lobes) lends some support to Jung's suggestion, which is a theoretical possibility and must not be overlooked. Nevertheless, the explanation of *all* frontal and precentral alpha activity by Jung's hypothesis requires complicated assumptions as to shifting foci of alpha activity which seem to us implausible. A more detailed discussion is beyond the scope of this paper, as the problem of *source* of alpha or any other type of wave in no way affects the empirical classification, evaluation and interpretation of EEG patterns, which is our present concern.

Alpha index. The alpha index is the percentage of time the alpha frequency appears in the monopolar occipital record, at a level 2 cm. above the inion (Davis, H. and Davis, P. A., 1936). The broadly tuned 10-cycle filter greatly facilitates the measurement. At least one (preferably more) standard length of 100 cm. of record run at 3 cm. per sec. and taken under standard conditions at least 10 sec. after the eyes have been closed is chosen. The alpha index is the number of centimeters occupied by the alpha rhythm in such a sample. The frequency of the alpha rhythm of an individual rarely varies more than 2 cycles. If his alpha frequency is 10 per sec. it may speed up 1 or at most 2 cycles following "eyes closed." Often it helps to get the alpha range by counting the first train of waves (average frequency of the

[5] Rubin does not specify precisely the frequencies which he calls the alpha rhythm.

first second) following "eyes closed" *if* they come in within the first half-second. This is the upper limit. Two cycles below this upper limit defines the lower limit. We arbitrarily include only those alpha waves appearing in trains of at least three waves, all of them 7 μV. or more from peak to trough.

The alpha index was the first objective measurement of the EEG by which subjects were divided into groups. We divided our first 50 subjects into 4 groups—the "dominant" being those with an alpha index from 75 to 100 per cent; "subdominant" from 50 to 75 per cent; "mixed" from 25 to 50 per cent; and "rare" from 0 to 25 per cent (see Davis, H. and Davis, P. A., 1936). The original 50 were almost evenly distributed, due to the small number of individuals, but our more recent measurements on a series of 400 "presumably normal" and "average" individuals (cf. p. 97) show a distribution with a definite peak at about 70 to 80 per cent (Davis, H., 1938; Davis, P. A. and Davis, H., 1939) and also confirm the approximate constancy of the index for a given individual over a period of years.

The alpha index was also measured on an "abnormal" series of 100 mental hospital patients (Davis and Davis, 1936). The peak in the distribution curve for this abnormal group was toward the lower indices, but measurement of this single factor alone did not differentiate an abnormal individual from a normal person.

Walter (1936) suggested "delta" as a generic term for slow waves. We use the term in a somewhat more restricted sense to include irregular wavelengths greater than 2.5 sec. or frequencies up to and including 4 per sec. (Davis, H., 1938).

Delta index. Hoagland introduced another measure which he called the "disintegration factor" (Hoagland, Rubin and Cameron, 1936) or "delta index" (Hoagland, Cameron and Rubin, 1937). Regarding the slow-wave activity (slower than alpha waves) seen in the EEG as a tortuous line, he traced its length in 100 cm. of record by means of a map measurer. The excess length of the line above 100 cm. he then designated as the delta index. He wished to measure the amount of slow-wave activity because of an impression that the frequency range below the alpha indicates abnormal physiological function. He applied his method to the records of schizophrenic patients in an attempt to find out whether the index correlated with the clinical status of the patient, but found no correlation between the index and schizophrenia. We measured the delta indices of our mental hospital group and compared the slow-wave activity with that of normals. The delta index was not a measure which would indicate the degree of clinical abnormality in a person, nor would it select the schizophrenic individuals from a mixed group.

The real difficulty with Hoagland's delta index, we feel, is that he attempted to measure abnormality which is represented both by irregular *voltage* and by long *wave-lengths*. These are two independent functions which do not bear the simple relationship to one another that the single figure of

the delta index implies. The abnormalities defy mathematical simplification. In the same length of record, a person having a large amount of very slow 1- and 2-cycle wave activity would have a lower delta index than another person having a lesser amount of 3- and 4-cycle activity of equal voltage. Yet the degree of abnormality represented by the 1- and 2-cycle range is often greater than that indicated by faster waves. We attempted to improve Hoagland's delta index by confining the measurement to a narrower range below 5 cycles, but still failed to find the measure valid. We called the measure so obtained the "delta excess" (Davis and Sulzbach, 1940).

Wellenindex. Jung (1939) also found the delta index unsatisfactory and devised instead his "Wellenindex," or wave index, which is the product of the greatest amplitudes and longest wave-lengths in a sample of record. Measurements are made in units of 100 μV. and 100 msec., and only such maximal amplitudes are considered as appear at least three times in 10 sec. The 3 maximal values are averaged if necessary. In healthy people, according to Jung, the wave index is generally less than 1, never above 1.5; in epileptics mostly above 1 up to 6, and in petit mal up to 30. In cases of brain tumor the wave index is less useful.

Measurement of coördination. Jung (1939) also undertook to measure the degree of coördination of different brain regions, particularly of the two occipital lobes with respect to alpha activity. Such measurement involved a statistical analysis of the phase relationships existing from time to time between the two sides of the head. No simple single "measure" or index has yet emerged from this study, but merely the statement that most "normals" show an "in-phase" relationship from 80 to 90 per cent of the time.

Grass-Gibbs frequency analyzer. Grass and Gibbs (1938) have developed a precise method for measuring the energy distribution as a function of frequency, but it is too early to judge its practical value. They have applied the method to the EEG's of many normal and abnormal individuals under varying conditions, *i.e.*, epilepsy, shifts in acid-base balance, sleep, etc. (Gibbs, Williams, and Gibbs, 1940). If amplification and sensitivity of the amplifiers are controlled, an accurate graphic representation may be made automatically of the distribution of energy throughout the spectrum in a given period of time (usually 30-sec. periods) chosen from the total record. This method is far more precise and objective than any method of subjective judgment based on visual inspection, even with the aid of broadly tuned filters. An important limitation, however, is that the analysis does not reveal the phase-relationships (wave-form) of the waves and their sequences in time. The method of analysis averages 30 sec. of activity and does not give any information as to whether the energy is produced by an even distribution throughout the 30 sec. or by a brief episode of extremely high voltage. This is important and will be discussed later. The frequency analyzer gives a separated series of static values to a dynamic progression of activity, but the method may well prove to be a valuable tool, particularly when selected features within sections of an EEG are to be studied.

Types of Electrical Activity

The accumulation of experience has led us to approach the problem of evaluation from still another angle, namely, observing the records in detail as a complex of inseparable and variable relationships. Frequencies and their relationships to one another, as well as voltage fluctuations, are studied. We now regard the complicated electrical activity as a *pattern* of electri-

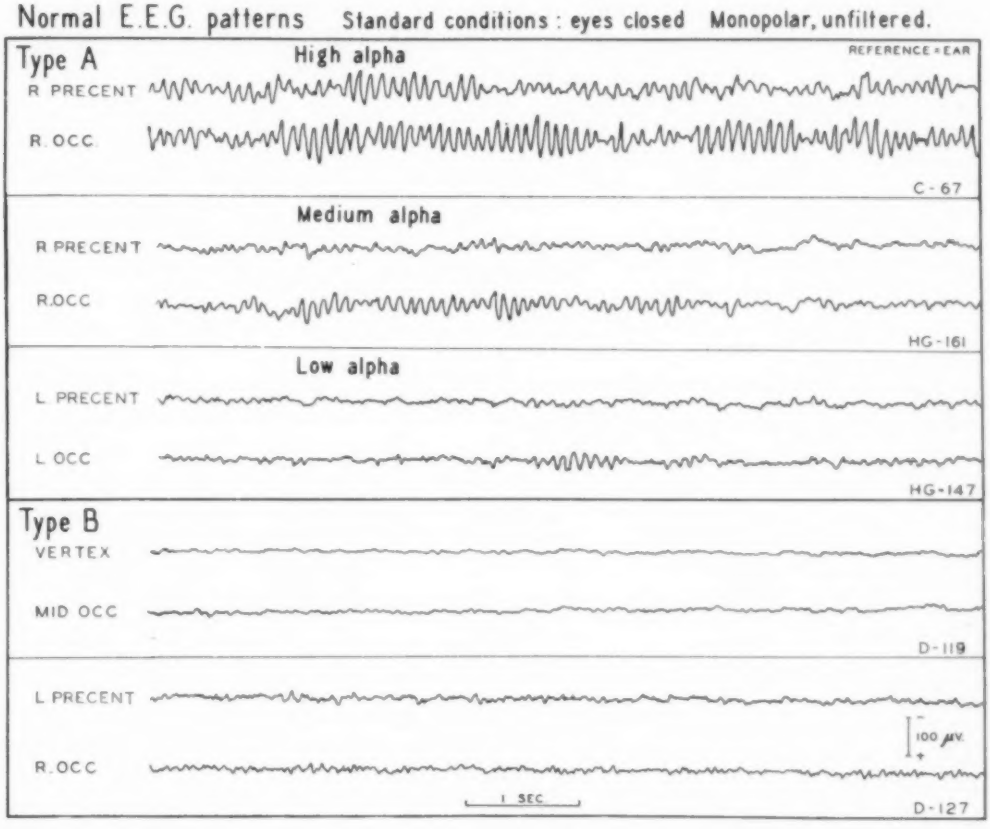

Fig. 2. In this and all subsequent figures, upward deflection indicates that electrode on head is electrically negative relative to reference electrode.

cal behavior rather than as a series of separate factors, in the same manner as one regards a person's behavior, attitude or personality as a pattern and not a series of separate factors.

Beta activity. The beta activity is a universal feature of all records and is present all over the living brain. It consists of short wave-lengths and fast frequencies (above 20 cycles). It represents physiological activity of the brain and is modified by physiological changes such as sleep. It is generalized, formless, low-voltage activity and serves as a rough background from which all patterns emerge. One can appreciate the beta activity of the brain

by observing the "residual occipital activity" when the eyes are open in a bright light. Under these conditions the alpha pattern is suppressed and makes clearer the beta activity. With experience it is possible to distinguish the beta activity from muscle potentials and from the "choppy" type of activity to be described below.

Patterns of electrical activity in normal individuals. Every individual when recorded under standard conditions reveals a pattern of electrical activity which is characteristic for him at his resting level. It must be emphasized that we are dealing with a dynamic physiological equilibrium and not a

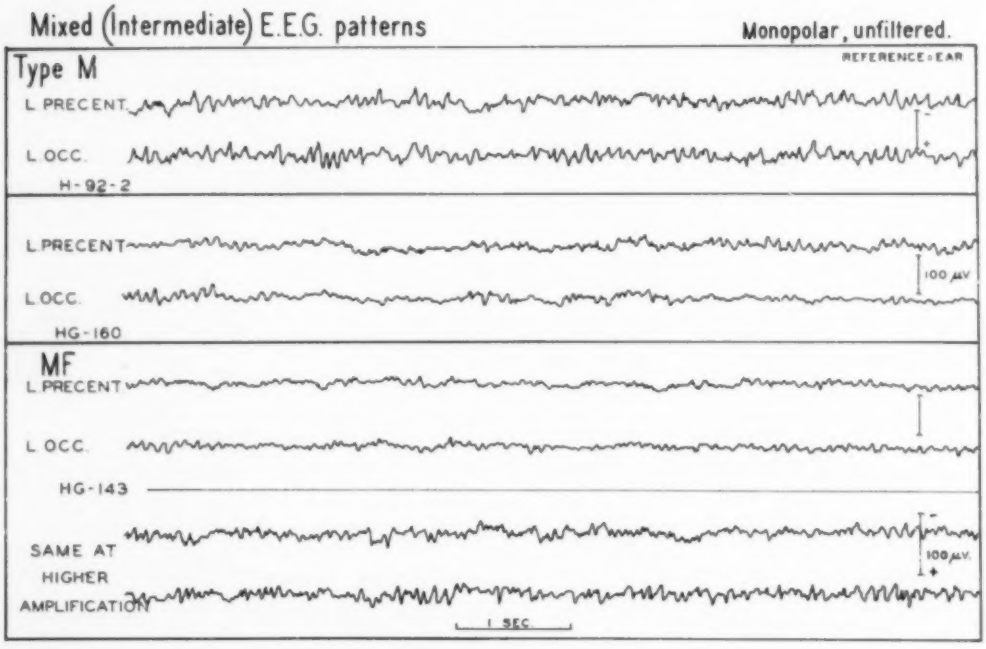

FIG. 3.

static condition. He may have an EEG of a high-voltage, predominantly alpha pattern or he may have a low-voltage pattern in which fast frequencies dominate. Whatever picture his EEG pattern presents, it maintains the same characteristics of wave-form, frequency range and voltage fluctuation upon repeated recording from one year to another, *provided* he is recorded under the same standard conditions.

A is the type of pattern (Fig. 2) which has a regular and clearly countable alpha rhythm which reveals a proportional distribution (cf. p. 101) over the occipital, precentral, and frontal areas when recorded simultaneously. Other frequencies in the pattern are consistent in their distribution and do not destroy the regularity of the alpha trains. The pattern may have a low alpha index and low voltage, for it is *quality* rather than *quantity* which is impor-

tant. The average voltage fluctuation of a typical *A* type of pattern is from 30 to 80 μV. Most *A* patterns have a characteristic voltage of 50 μV. or higher.

B is the type of pattern (Fig. 2) which under standard conditions and resting level of activity is made up predominantly of fast frequencies from 14 to 20 cycles which merge into the background of low-voltage beta activity. The average voltage fluctuation of a *B* type of EEG is from 10 to 30 μV., rarely higher. This type is rare but definite.

M is a type of pattern (Fig. 3) which is composed of mixed frequencies, none clearly dominant, but which includes such a wide frequency range that

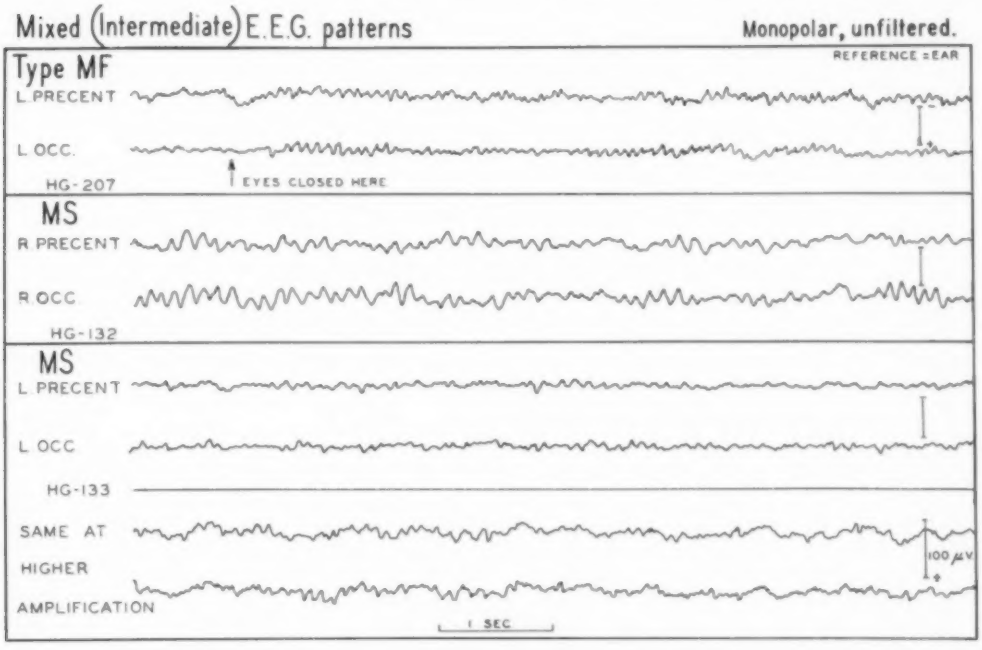

FIG. 4.

slow, alpha, and fast frequencies are all represented. The range of voltage is usually between 20 and 60 μV. The irregularity of the patterns in this group is in contrast to the uniformity and regularity of the *A* and *B* patterns.

MF indicates a mixture of frequencies (Fig. 3 and 4) in the alpha and fast-frequency ranges whose voltage fluctuates in a consistent manner within a narrow range. These patterns show varying amounts of alpha activity mixed with a fast-frequency component which tends to make the alpha wave-form sharp or irregular. The frequency of the alpha is usually over 10.5 cycles. The *MF* type of pattern is the commonest among normal individuals, although the *A* type is a close second.

MS is the counterpart of *MF*, and includes EEG's having a mixture of frequencies (Fig. 4) in the alpha and the slow-frequency ranges. These alpha

waves are likely to be in the 9- to 10-cycle range and slightly blunted or deformed by the interference of the slower frequencies.

If there is difficulty in making a decision between the *A* and the *MF* type, determining factors for *MF* are the departure from the proportional distribution and from the regular quality of the alpha activity over the various areas, and a greater prominence of fast or slow activity in the precentral and frontal regions.

These groups, *A*, *B*, *M*, *MF* and *MS*, are regarded as normal when they maintain a consistent stability of voltage and frequency range for their type. The divisions between these groups are arbitrary and often difficult to determine, because the quality of variability by its very essence precludes a rigid classification.

General Types of Abnormality Seen in the Electroencephalogram

As one studies EEG patterns over a long period of time, it becomes increasingly clear that as a pattern becomes less organized it becomes less normal (Fig. 7). This statement is based on many observations in which the

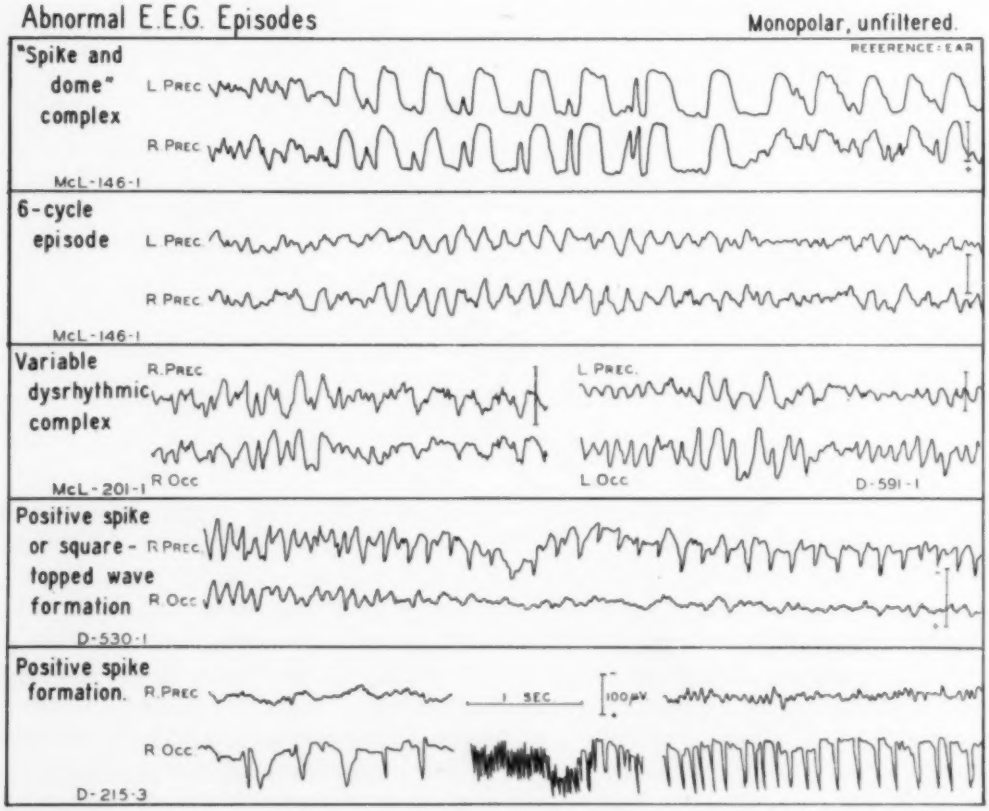

Fig. 5. Types of abnormal activity seen among mental patients. These examples represent *transient* abnormal physiological behavior of the brain.

clinical condition of the individual has been correlated with the modifications of the EEG. As the instability becomes exaggerated, the pattern begins to break up into episodes (Fig. 5) which involve a remarkable assortment of configurations made up of extremes of frequency, voltage, or exaggerations of one or few frequencies, usually outside the alpha range.

The type of disturbance in one or more regions of the brain determines the significance of the abnormality.

"*Choppy*" *type of activity.* This is an abnormal, formless pattern which looks like beta activity at increased amplification on a slower tape (Davis,

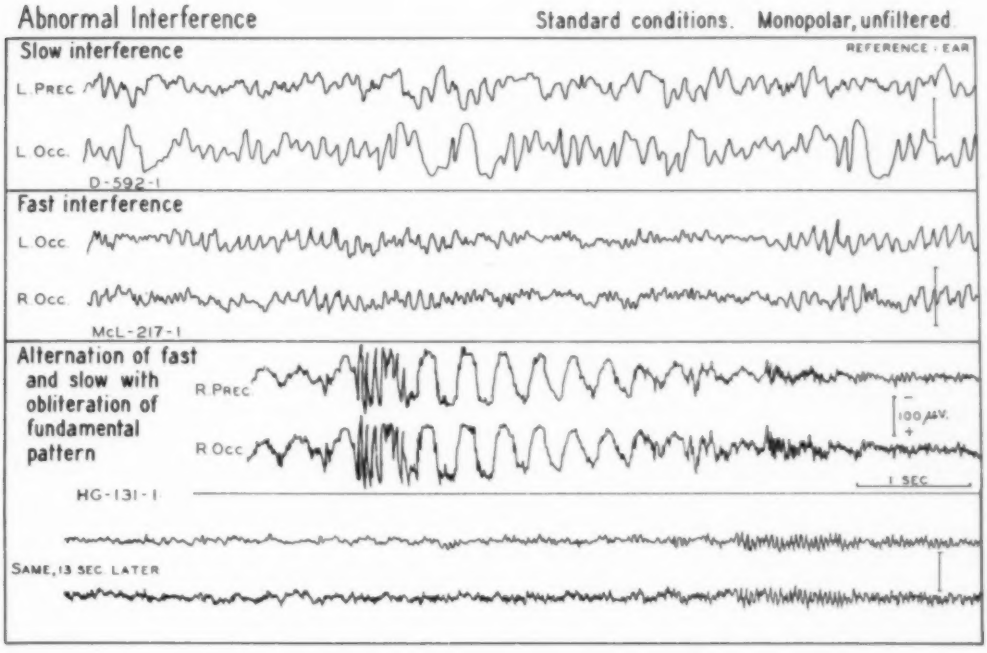

FIG. 6.

P. A., 1940). For two years this quality in the record was confused with muscle potentials. We felt that it was not due to muscle potentials, because after using every means at our disposal to rule them out the pattern still remained in certain cases. Finally, with hospital patients upon whom pneumoencephalograms or x-ray plates were made, it was possible to show that this "choppy" activity was associated with regions of gross cerebral lesion. If it were muscle potentials, other leads in corresponding areas on the opposite side of the head should have at least occasionally revealed the same type of record. One record on an individual may not be enough to determine whether the "choppy" quality represents muscle potentials or whether it is due to cerebral lesion. One must use bipolar as well as monopolar recording, compare corresponding areas of the head and use every precaution to rule

out artefact or muscle potentials. The "choppy" quality has been seen only very rarely outside the hospital, and at present we feel that it indicates cerebral damage.

Dysrhythmic type of activity. The dysrhythmic type of abnormal interference includes the *well-known abnormal complexes* (Fig. 5 and 6) which may appear and disappear in the EEG. It may be well organized (Fig. 6, HG-131) or unorganized (Fig. 6, D-592; Fig. 7), or it may appear as a variant which never establishes itself clearly as a well-organized interference (Fig. 5, secs. 3, 4). "Dysrhythmia" implies disturbance of the normal rhythms of the brain; it does not imply an arhythmia or necessarily an irregularity in trains of waves. It is used here in the sense that Gibbs, Gibbs and Lennox

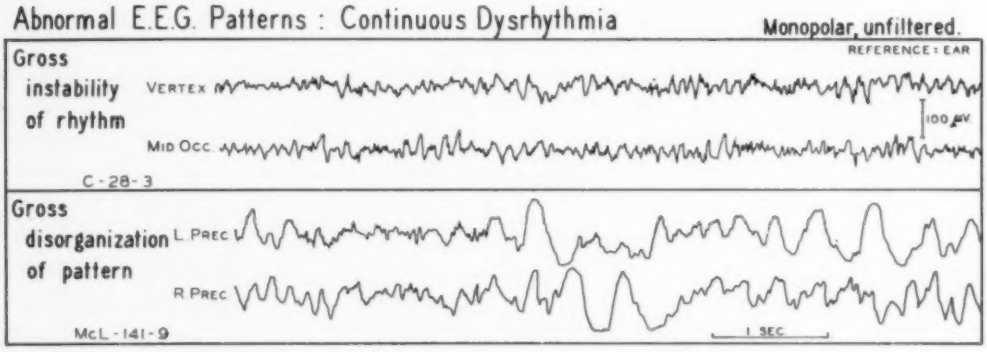

FIG. 7. Two examples of continuous dysrhythmia. The first represents gross instability which interferes with but does not destroy the fundamental pattern. Electrical filters introduced into the recording circuit would reveal more clearly the fundamental alpha pattern of this EEG.

The second EEG represents gross disorganization, in which the alpha activity is replaced by the delta activity which destroys the fundamental pattern.

(1937) employ it in describing the unusual patterns recorded in "psychomotor" attacks and other epileptic seizures.

The dysrhythmic types of abnormalities may be listed as follows:

(1) *Localized slow-wave activity* is observed in the region of tumors or other gross lesions.

(2) *Episodes of "locked patterns"*[6] include the "spike-and-dome" complex, often associated with petit-mal, the minor seizures of epilepsy with brief lapse of consciousness (Fig. 5, first 2 lines), and the organized trains of waves of fast frequency and of high voltage, usually characteristic for grand-mal or overt convulsive seizures. The less clearly organized episodes of fast, positive-spike, or square-topped waves (Fig. 5, secs. 3, 4, 5) are observed in all types of epileptic seizures, but are perhaps more commonly seen in relation to attacks of confusion, fugues, behavior disorders and atypical motor attacks (types of seizures all combined under the title of "psychomotor" by

[6] "Locked pattern" is a term defining a dysrhythmic combination of wave complexes which follow each other in organized sequence.

Gibbs and Lennox). These EEG patterns are not as well organized as the "locked patterns." In fact, any specific frequency (Fig. 5 and 6) interfering with the characteristic normal pattern may constitute an episode.

Such abnormal activity indicates a temporary disturbance of physiological function. Correlation of some of these formations with behavior or symptoms is so striking that their appearance in less organized form, without clinical symptoms, is important.

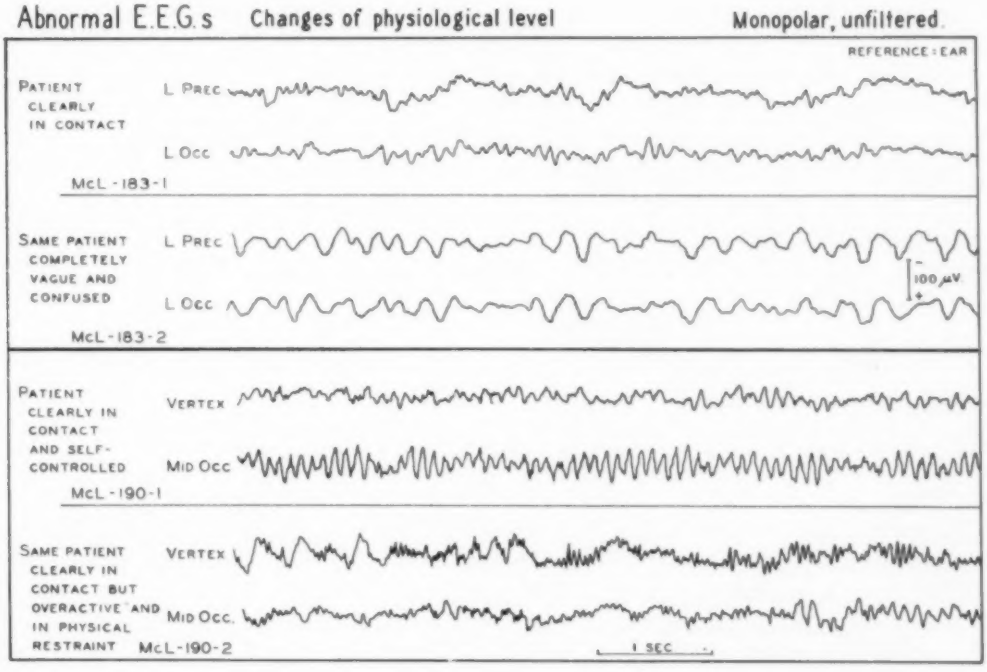

FIG. 8. Abnormal EEG's of 2 mental patients. McL-183 shows delta activity which is associated with impaired consciousness at the time of recording. "In contact" implies that the patient is aware of and responsive to his immediate environment.

McL-190 shows fast-frequency activity replacing the alpha and maintaining itself in the presence of delta waves. This electrical activity is associated with clinical overactivity at the time of recording.

(3) *Continuous generalized dysrhythmia* may continually distort the EEG to such an extent that the characteristic pattern of the person is *never free from the distortion* (Fig. 7 and Fig. 6, D-592). The transitions from the normal EEG to the abnormal EEG are many. *Episodes* are periods in which there is a transition sharp enough to stand out clearly from the characteristic pattern (Fig. 5), or a gradual build-up into a frequency range of voltage change sufficient to differentiate or delimit the activity from the rest of the record (Fig. 6). Episodes may make the characteristic pattern abnormal only temporarily. On the other hand, an inherent disorder in the mechanisms

which modifies the activity of the cortex may continuously interfere with the establishment of a normal pattern (Fig. 7).

It is known that under 10 years of age children's patterns normally tend to have slower frequencies and are more unstable than those of adults. Therefore, if one is to understand the significance of variations in patterns, it is important to know at least the approximate age of the person when evaluating an EEG, as well as to have had experience with different types of EEG.

An EEG is a record of continuous activity fluctuating within certain narrow limits of frequency and voltage. When, under standard conditions of recording, the EEG fluctuates beyond a certain point and the frequencies reveal a spreading or clumping in some unusual manner it is an indication of greater instability of physiological activity (Fig. 5, sec. 3, 4, and 5; Fig. 7, sec. 1). From rambling low-voltage abnormal activity, creeping into and disappearing from a record, to the recognized specific complexes which are organized as "locked patterns" (Fig. 5, sec. 1, 2, 4, 5), one may observe every gradation in quality, relationship, and degree (Fig. 7 and 8).

Evaluation of the Total Record

In the Department of Physiology at the Harvard Medical School and the electroencephalographic laboratory of the McLean Hospital we have been studying the mechanisms underlying these abnormal complexes which break into the individual characteristic pattern. Disturbances in the fundamental mechanisms of the brain sometimes completely obliterate the pattern, as in the epilepsies, or only modify it locally, as in focal cerebral lesions. Experience and detailed study of the conditions under which they appear or can be produced must be the basis of evaluation.

Certain alterations of electrical pattern are correlated with particular types of alteration of behavior. The alteration of behavior may be overactivity (see Fig. 8, last 2 lines), or a greater retardation of activity (Fig. 8, first half). Slow and fast frequencies, which may occur singly or combine to form a complex or particular pattern of their own, are often associated with overt behavior disturbances. Many epileptic patterns, especially the "spike-and-dome" complex, represent a combination of fast and slow waves (Fig. 5, sec. 1, 3, 4, 5). The important factor is the *change of electrical activity* from what is normal for the individual. The *changes in quality* of electrical activity constitute a basis of evaluation.

A gross analysis of the EEG recorded by routine placements has been standardized (Table 2).

Rating the record on a five-point scale. The basis of ratings is not specifically frequency or voltage. It is based on the quality of the pattern as a whole, particularly as to its general stability, regularity of wave-forms, and the type and amount of variability or interference if any.

Rating 1 is given to any normal type of pattern which is stable in its fluctuations of frequency and voltage within fairly narrow limits and without

any sharp transitions. The pattern of each area is consistent throughout the record and there is an approximate similarity of patterns and voltages in the two hemispheres. The patterns in the different areas bear the usual relationships to one another (see p. 108).

Table 2. Tabular headings for gross analysis

Serial no.	Type of pattern	Volt.	Reg.	Alpha		Resp. to "O & Cl"	Asymmetry	
	A, B, M, MS, or MF	Ave. (+) High (++) or Low (−)	Ir., Int., or Reg.	Per cent	Freq.	Good (+) Poor (−) or Ir.	Yes (+) No (−)	More α on right or left

Abnormal activity					Freq. band of Dysrhythmia			Location of Dysrhythmia	Rating	Remarks
E	R	Sp.	Diff.	Local	δ 1–3	SF 4–8	FF 16+	If not diff. give the order of prom. by area	Based on total record	

Key

Ir. = irregular, meaning frequencies are irregular and distorted.
Int. = interference, meaning good wave form but other frequencies interfere with its appearance or superimpose themselves.
Reg. = clearly regular without distortion or superimposed frequencies.
Alpha per cent is measured on 100 cm. of record.
Alpha frequency is counted and determined from speed-up following eyes closed (see text).
Resp. to "O and Cl" is appearance of alpha following eyes open and closed. Slight delay in response is secondary.
Sp. = specifically recognized complex such as petit-mal or grand-mal complex. complex or variant.
Diff. = diffuse.
Local = localized to an area or side.
E = episodal dysrhythmic interference.
R = "rambling" dysrhythmic quality as opposed to clear episode, usually in the slow range.

Rating 2 includes normal records which are slightly less stable or regular than those rated 1, and which may fluctuate in a somewhat atypical manner or which have an alpha rhythm that is regular but unusual in wave-form. If in an otherwise normal record there are *atypical* eye-movement patterns, which may or may not be due to movement artefact, when the eyes are either open or closed, it rates as 2.

Rating 3 includes normal records in which some feature may be exaggerated and yet which cannot in itself be regarded as abnormal. The *M* group of patterns are often rated as 3 because of the quality of instability, alteration of frequency and distortion of wave-form. Rating 3 is also given to unusual records which are atypical but about which nothing is known defi-

nitely enough to classify them as abnormal. A record rated as 3 is different from normal records, yet so free from any specific known abnormality that it is placed on the borderline until further knowledge gives us a clue as to how it should be classified. A pattern in which more alpha frequency appears on the frontal area than on the occipital area,—everything else being equal,—would rate as 3. The record as a whole and the relationships of the activities in all recorded areas must be regarded.

Rating 4 is given to any record which is dysrhythmic and suspicious and has recognized abnormal qualities clearly indicated, but no feature typical or

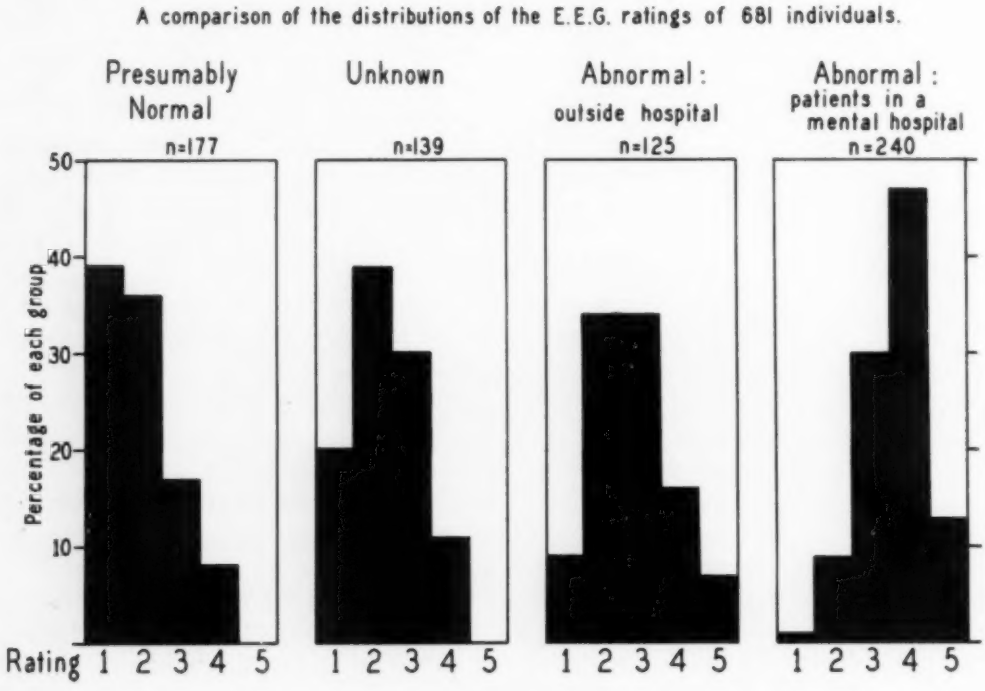

FIG. 9.

outstanding enough to warrant definite diagnosis. Included in a group rated as 4 would be many patterns which have irregularities maintained for very short times or contain waves or formations which are outside normal limits but not sufficiently organized to be characteristic of definitely abnormal episodes. The irregular and unsteady quality of such a record becomes in itself the dominant characteristic rather than any one particular feature or the sum of a group of features.

Rating 5 is given to any record which reveals recognized abnormal dysrhythmias, such as those found in epilepsy (Gibbs, Gibbs, and Lennox, 1938a, b). The abnormalities must be specific and well known. "Choppy" records, especially if obtained from all leads and controlled by tests to rule out artefacts, would be rated as 5. If slow waves can be localized such as those suggestive of a tumor or other gross lesion, the record would be rated as 5.

These ratings involve a consideration not only of the type of abnormality seen in the EEG but particularly the factor of stability, which is an essential characteristic of ratings 1 and 2, and the factor of instability characteristic of ratings 4 and 5.

Even *within* a group of known abnormals such as a group of schizophrenics (Davis, P. A., 1940) it was shown that the factor of stability and instability correlated with clinical behavior. Normal stable patterns were correlated with stable behavior, although stable behavior does not here imply normal behavior. Dysrhythmic patterns were correlated with unstable behavior.

Validation of the rating system. The EEG's of the groups of normals, presumably normals, unknowns and abnormals were rated, the groups being mixed and the EEG's given numbers so that the identity of the individuals was unknown. The author re-rated 121 EEG's and agreed with her previous ratings to within 1 point in all but 7 cases. A second judge, Dr. H. Davis, agreed to within 1 point with the author in all but 21 of 134 cases, and within 2 points in all but 2 cases.[7] There was complete agreement on the cases falling in the extremes when all EEG's containing episodes which might be artefact were eliminated. In no case was there a shift in the rating from normal to abnormal, or *vice versa*.

Only 14 individuals met all the requirements of the classification of "selected normal." It is significant, however, that both judges independently and without any knowledge as to their identify or classification gave their records all a rating of 1. This group was so small they were added to the "presumably normal" group.

The data validate the system of measurements presented in this paper. The peak of the distribution curves (Fig. 9) shifts systematically from 1 to 4 as we go from the normal to the abnormal group. No EEG's in the groups of normal and unknowns are rated as 5, which is the rating given to an EEG which we consider diagnostically abnormal. There are a few, but only a few, EEG's rated as 1 in the abnormal groups. The correspondence between our ratings of the EEG's and the groupings of the individuals validates the criteria of normality and abnormality of the EEG.

The graphs show an overlap in the ratings. Further study may reveal the reasons and significance of this overlap. Hereditary factors in epilepsy (Löwenback, 1939; Lennox, Gibbs and Gibbs, 1939; Strauss, Rahm and Barrera, 1939) offer an important lead in this direction. It explains the rating of 4 in a number of individuals considered clinically normal, for some of them have epileptic parents or blood relatives. These normal people carried the same abnormal qualities in their EEG's which are seen between seizures in the EEG's of known epileptics.

Discussion

There is some overlap of the *A*, *B* and *M* types of pattern. The extremes, however, are clear. The *A* type of pattern is different from the *B* and *M*

[7] The ratings were first made on a 9-point scale as follows: 1, 1a, 2, 2a, 3, 3a, 4, 4a, 5. A 1-point difference exists when ratings 2 and 3, or 2a, and 3a, appear for the same record, but 2 to 2a, or 2a to 3 are only half-point differences.

types in spite of the fact that the brains revealing them are apparently normal. Human beings are equipped with similar physiological mechanisms and gross anatomical structure, but this does not imply that the brains will respond in similar manner.

The EEG reflects the behavior of the brain as it maintains its level of activity in its internal environment. The internal environment is kept rela-

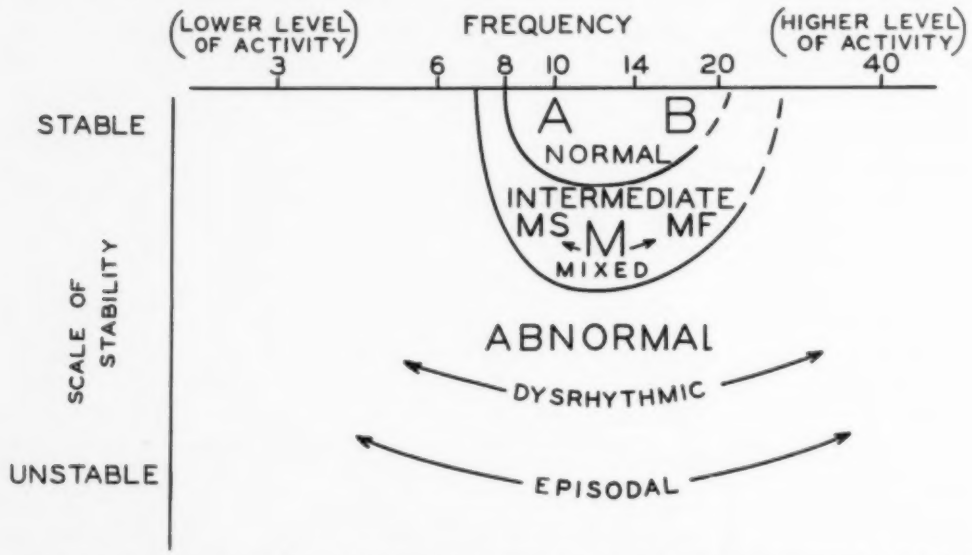

FIG. 10. Schema of the physiological activity of the brain as expressed by EEG patterns in terms of normality, stability, and frequency.

Although most frequencies are represented in all EEG's, certain ranges stand out most clearly in a particular record, and place the type of pattern in this schema. The gradation from normal to abnormal involves a wider spread of the frequency range and at the same time a tendency to greater instability. When a record is more confused with slow frequencies there is usually a distinct shift toward disorganization and breakdown of frequencies into irregular waves or complex formations (lower left quadrant). When the higher frequencies are involved there usually is a tendency toward greater organization and regularity (upper right quadrant). Correlated with these extremes, there is at the slow end impairment of consciousness from a depressed physiological activity and at the fast end physiological overactivity which may eventually lead to exhaustion with resulting impairment of consciousness.

This schema includes only two dimensions of a multidimensional schema which is in the process of development.

tively constant by the familiar mechanisms of homeostasis. If the internal environment of the brain is modified, the EEG will reflect the change, but brains have different resting levels of activity. It should be stated here that these levels of activity do not appear in any way to be related to intelligence, as the word is commonly used.

Figure 10 represents certain aspects of the physiological activity of the brain, as expressed by the various types of EEG patterns, in terms of stability, frequency and normality. It is intended to express graphically our generalizations that the unstable dysrhythmic or episodic records are abnor-

mal and also that a record whose most prominent frequencies are very fast or very slow is likewise abnormal, even though the pattern may be well organized and stable.

If the anatomical structure of the brain is damaged or its physiological or chemical condition is modified to the extent of altering the state of consciousness the EEG will be modified (Davis, H. and Davis, P. A., 1939). The general types of abnormal electrical activity have been described in order that the significance of disturbances of physiological function may be appreciated when evaluations of the EEG's are being made. Moreover, a relation between a person's EEG and his characteristic behavior has been found (Davis, P. A., 1940). Types of normal EEG's and their modifications are being related to subtle changes in behavior of the individual as well as to the more fundamental psychological organization of the personality (Saul, Davis and Davis, 1937; Davis, H. and Davis, P. A., 1939).

Summary

The measurement of specific features of the EEG is described. The limitations in measuring single factors, and of synthesizing them, is pointed out. A system of evaluating the EEG pattern as a whole on a 5-point scale from normality to abnormality is described (p. 108). The underlying quality of stability versus instability of pattern is the basis of this system of evaluation.

Normal patterns are divided into types as follows: *A* patterns (Fig. 2) are dominated by regular alpha sequences which are clearly countable. *B* patterns (Fig. 2) lack alpha sequences when subjects are run under standard conditions. *M* patterns (Fig. 3) include EEG's which are composed of mixed frequencies. This latter group is subdivided into the *MS* group (Fig. 4), in which the slow waves are responsible for the mixed frequencies, and the *MF* group (Figs. 3 and 4), in which the fast frequencies are prominent. The *M* group, though regarded as normal, appears to be intermediate between the normal and abnormal.

The abnormal features of the EEG known at present are described as "episodal" (Fig. 5) or as "continuously dysrhythmic" (Fig. 7). They include every gradation of dysrhythmia up to the well-recognized epileptic patterns; the "choppy" quality obscuring a normal pattern (shown to have been associated with brain damage in three cases); and localized slow-wave activity associated with tumors or focal lesions. These features are discussed in relation to the evaluation of an EEG (p. 105).

The importance of the technique and procedure of recording and the necessity for standard conditions are emphasized.

The method has been validated on selected groups of adult individuals which are compared with one another, such as a known normal group, a presumably normal or average group, and known abnormal groups (Fig. 9).

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ACTIVITY IN NEURONS OF THE BULBOSPINAL CORRELATION SYSTEM*

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THIS STUDY is concerned with the descending spinal projections of bulbar and spinal nuclei. These find their anatomical expression chiefly in the vestibulospinal, reticulospinal and propriospinal tracts. It is certain from anatomical studies that stimulating electrodes placed in the floor of the fourth ventricle excite neurons of the vestibular and reticular systems (Gray, 1926; Papez, 1926; Lorente de Nó, 1938c). A diagram of vestibuloreticular connections and their ascending projections has been presented by Lorente de Nó and Berens (1939, Fig. 4). Stimulating electrodes, placed within the ventrolateral columns of the spinal cord, excite not only the spinal projections of the vestibuloreticular complex, but also neurons of the propriospinal system which arise at, or cephalad to, the site of the electrodes (Sherrington and Laslett, 1902, 1903†).

The results of stimulating these bundles have been recorded by the use of microelectrodes placed either in the tracts themselves, or in the gray substance, and by leads placed either on ventral roots, or on the peripheral plexuses, to record the discharge of motoneurons. The first attempt to obtain records of the activity of the spinal cord and associated nerves following stimulation of the cord itself, was made by Gotch and Horsley (1891). Working under many handicaps that have been remedied in the intervening 50 years, these investigators observed only the slow potentials which may be recorded from the surface of the cord as a result of tetanic stimulation. Some of their original observations have been repeated during the course of the present investigation. However, the observations reported here deal with the more rapid and detailed responses observable with single shock excitation, which unavoidably escaped the attention of Gotch and Horsley.

Cats have been used throughout the experiments. The preparations have been decerebrate, decerebrate spinal, or spinal, or lightly narcotized with dial (usually 0.5 ml/kg.) or nembutal (25–30 mg/kg.) with or without subsequent spinal section or decerebration. The observed differences in these preparations were largely quantitative, and were probably related to the intensity of tonic vestibular background.

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* A preliminary account of some of the present results was presented at the meeting in New Orleans of the American Physiological Society (Lloyd, 1940).

† Extracts from this classical paper are reprinted in *Selected writings of Sir Charles Sherrington*, compiled and edited by D. Denny-Brown, New York, Paul B. Hoeber, 1939, xiv, 531 pp. (see pp. 201–224).

Conduction in bulbospinal and propriospinal tracts

The records reproduced in Fig. 1 show the response of the ventrolateral columns to a single shock delivered to the floor of the fourth ventricle at each of several conduction distances varying between 3 and 29 cm. The characteristic response consists of two spike potentials separated by an interval of 0.9 msec. In other preparations this interval has varied from 0.7 to 1.0 msec. Although the latency to the first spike potential increases with the conduction distance, neither of the two spike potentials suffers appreciable temporal dispersion, nor is the interval between the spike potentials increased, even after conduction through the whole length of the spinal cord. These facts are consistent only with the interpretation that conduction is occurring in two groups of homogeneous fibers of alpha velocity, separated in time by an interval characteristic of a single central synaptic delay (Lorente de Nó, 1935a; 1938a).

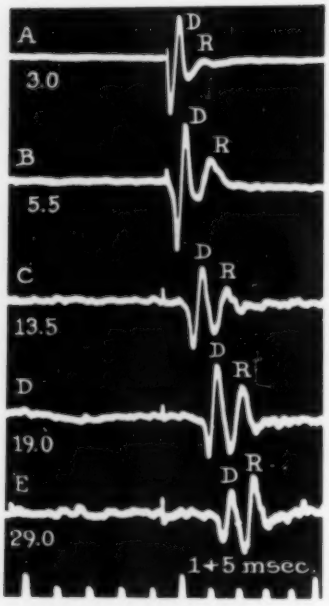

FIG. 1. Bulbospinal preparation. Activity in the ventrolateral column recorded at various levels of the spinal cord by a microelectrode placed in the column. Stimulus, a single shock to the floor of the fourth ventricle. Conduction distance in centimeters is indicated for each record by the figure at the left. D, signifies the directly conducted alpha spike potential; R, the synaptically relayed alpha spike potential. Time in 1 and 5 msec. intervals is shown at the bottom. In all the figures where there are two time designations, these are for the small and large divisions respectively.

Further evidence that the second spike potential of the column response is recorded from neurons excited transsynaptically is found in Fig. 2. In this experiment the stimulating electrodes were placed in the lower thoracic cord in a way so as to stimulate fibers of the ventrolateral columns. The recording microelectrode was placed in the column of the lumbar cord 9 cm. aborally. Two shocks, separated by an interval of 2.5 msec., were delivered. In Fig. 2A, the characteristic double spike potential response which follows each of the two shocks is seen. The second or relayed spike potential of the response to the second shock is increased by facilitation. Other examples of the facilitation of the relayed spike potential may be seen in Fig. 7 and 8. The relayed spike potential is rapidly abolished by a period of asphyxia too short to decrease or disperse the initial spike potential appreciably. Figure 2 (B and C), otherwise identical with Fig. 2A, shows two stages in the effect of asphyxia on conduction through the ventrolateral column. A completely differential and rapid loss of excitability such as this is characteristic of central synapses, rather than of different fiber components directly stimulated but suffering dispersion by conduction.

The sequence of two spike potentials is seen in the ventrolateral columns, whether the regions selected for recording be cervical, thoracic, lumbar or sacral, and whatever may be the conduction distance allowed. This fact has been confirmed with shocks delivered to the floor of the fourth ventricle and to all the regions of the spinal cord. Records obtained by employing a number of conduction distances in a single preparation (Fig. 1) indicate that there is a roughly linear relationship between the conduction distance and the ratio

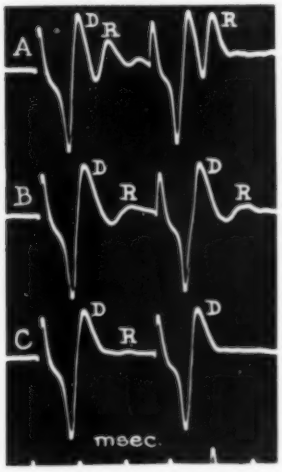

FIG. 2. Thoracolumbar preparation. Facilitation and asphyxial blocking of the synaptically relayed spike potential, R. Two identical shocks were delivered to the ventral column of the lower thoracic cord. Recording by microelectrode in lumbar ventral column. Conduction distance, 9 cm.

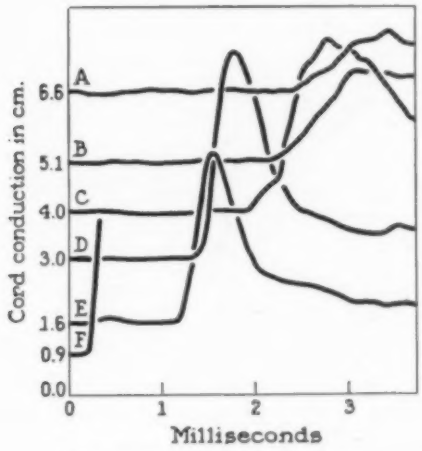

FIG. 3. Response of the first sacral ventral root to ventrolateral column shocks. Ordinates, distance of stimulating electrodes cranial to middle of first sacral segment in centimeters. Abscissae, time from shock artifact in milliseconds. The motoneuron responses were projected from the original records onto these coordinates and copied. A, B, and C were recorded at 5 × amplification for D, E, and F. Hence responses are much smaller and less synchronous in A, B, and C.

of synaptically relayed activity to unrelayed activity. Sectioning the neuraxis immediately cranial to the stimulating electrodes proves that the relayed spike potential must arise aborally from the stimulating electrodes. The relayed spike potential, furthermore, is recorded from the white substance itself, and is conducted in the same sense as is the initial spike potential. Hence the structures from which the second spike potential is recorded are propriospinal neurons, although when the stimulating electrodes are placed in the fourth ventricle, some reticulospinal elements may be contributing to the second spike potential.*

* The distinction between reticulospinal and propriospinal neurons is as artificial as is the division of the central nervous system into brain and spinal cord. The retention of the distinctive terms is justified at the present time on the basis of common usage.

There must be a fairly even distribution of the propriospinal somata along the long axis of the spinal cord to account for the regular increase with conduction distance in the relayed spike potential relative to the initial spike potential.

Emphasis must be placed on the fact that no critical evidence as to the axial length of the relay neurons can be drawn from experiments employing tract conduction. For instance, it would be possible theoretically to record both direct and relayed spike potentials with the conduction distance reduced to but a few millimeters, even though all the responding neurons had axial lengths of many centimeters. On the other hand, relatively satisfactory evidence has been obtained by recording the discharge of motoneurons in response to column shocks delivered at different distances from those motoneurons.

In Fig. 3 are shown the motoneuron discharges in response to ventral column shocks set up at several distances from the middle of a segment, the ventral root of which was used for recording. The individual records are arranged so that in effect cord conduction distance (ordinates) is plotted against latency of response (abscissae). In A, B, and C the amplification used was five times that for D, E, and F. The latency in F (0.2 msec.) is the ventral root conduction time, since the motoneurons are stimulated directly. In E there is a small direct response of the motoneurons, but the majority are now excited to discharge a nearly synchronous volley with a steplike additional latency of approximately 1.0 msec. This added latency is in a large part the synaptic delay at the motoneurons, though some cord conduction time must be included. In D, with 3 cm. cord conduction, the direct response is abolished, while the latency of the synaptically relayed response is increased to approximately 1.35 msec. The additional latency of D over that of E (0.15 msec.) accounts only for additional conduction time at the velocity of alpha fibers. Thus the responses shown in D, E, and F are similar in nature to the *M* and *S* waves recorded by Lorente de Nó from the oculomotor preparation (1939, p. 409, Fig. 4). The responses A and B are much smaller and less synchronous than those in D and E. A line drawn to join the points of onset of the motoneuron discharges in records A and B is closely parallel to a similar line joining the points of onset of the motoneuron discharges in records C and D, but it is later by approximately 0.7 msec. in the time axis. This is interpreted to mean that an additional neuron has been introduced into the shortest *effective* pathway to the motoneurons at conduction distances greater than 5 cm. In other experiments similar to the one detailed here the responses of the motoneurons with cord conduction distances greater than approximately 3.5 to 4 cm. have been still further delayed (for example, see Fig. 7A) or were even absent, unless they were preceded by another similar volley, in which case facilitation brought in a response with latency comparable to that of A and B of Fig. 3, but never comparable with that of D and E. The variability in unconditioned responses in different preparations is related to the general excitability of the individual preparations.

Record C of Fig. 3 illustrates an effect which has been encountered occasionally with conduction distances between 3 and 5 cm. The rising phase of the spike elevation has two parts. The onset of the main elevation, obtained by extrapolation of its rising phase down to zero potential, falls exactly on the plot of latency of responses A and B. The small initial elevation, partially fused with the main elevation, has a latency intermediate to those of B and D, and is closer to both than the minimal time allowable for a synaptic relay (Lorente de Nó, 1938a). Since it is not possible that the pathway for response B can be more than one neuron longer than that for D, the best available interpretation for intermediate latencies, appearing when a critical length of cord is traversed, is that they are the result of the summation of impulses in the slowest conducting pathways having one synaptic relay, with those in the fastest conducting pathways having two synaptic relays. Specific differences in individual synaptic delays within the relatively fixed limits established by Lorente de Nó (1938a) could aid in producing this effect.

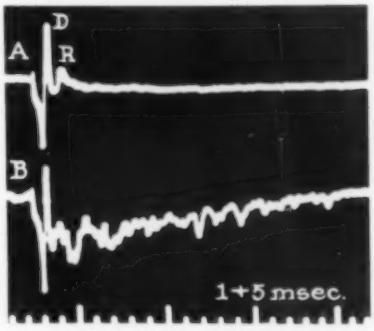

FIG. 4. Lumbar preparation. Comparison of white column and gray substance responses to a single ventrolateral column shock. A, recorded by microelectrode in ventral column; B, recorded by the same microelectrode placed in the ventral gray horn.

Thus, when the stimulating electrodes are placed within 3 or 4 cm. of a motoneuron pool, the motoneurons discharge following the direct tract volley; when at longer distances the motoneurons discharge only after the arrival of the relayed tract volley at the pool. Therefore, for the alpha-tempo conduction pathways of the ventrolateral columns, leading to the motoneurons, the relay occurs at a mean distance of about 3.5 cm. These neurons intercalated in the shortest *effective* pathway to the motoneurons from more cranial regions of the spinal cord, or reticular formation, are obviously short propriospinal neurons (short spinal association neurons of Sherrington and Laslett, 1902, 1903). It must be noted here that the present method of indicating the axial length of the relay short propriospinal neurons demonstrates only the maximal distance at which sufficient of the shorter propriospinal neurons are excited directly to effect the discharge of motoneurons with only one synaptic delay. Therefore, it cannot be denied that many of the short propriospinal fibres will be shorter than this. On the other hand, it is shown below that much longer descending fibres enter into synaptic relation with the motoneurons. There is, therefore, no indication that the short propriospinal fibres occupy the position of specialized but true "Schaltzellen" in the sense of von Monakow (cf. Cajal, 1911, p. 150). Conversely, there is no experimental proof here that some do not.

It is unlikely from the direct evidence of tract conduction that many of the alpha pathways from superior to inferior regions of the spinal cord

employ more than two axially orientated neurons lying within the white columns. Hence the typical large celled internuncial pathway may be considered as including a long propriospinal or bulbospinal neuron, which has feeble endings on motoneurons, with powerful collaterals to short propriospinal neurons. These latter have, in turn, endings on the motoneurons.

Response of the gray columns

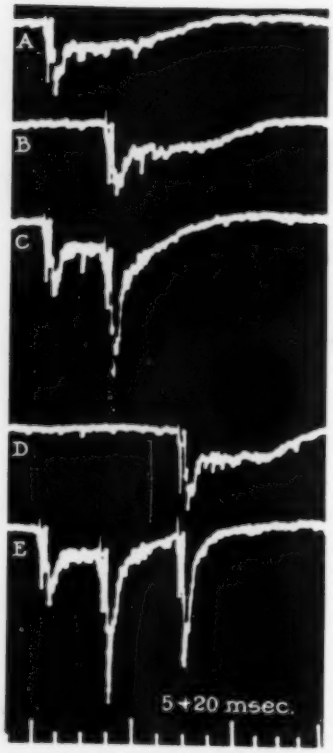

FIG. 5. Lumbar preparation. Response of the gray substance, recorded by microelectrode placed in ventral horn, to repeated stimulation of the ventrolateralcolumn. A, B, and D are the responses to the three column shocks in isolation. In comparing C with A and B, and E with C and D, note channeling of activity through shorter interneuron chains by virtue of previous activation of the pool.

While the activity of the ventrolateral white columns, as recorded by the microelectrode, stops abruptly following the completion of the double spike potential complex set up by a single shock, a microelectrode in the gray substance, by contrast, reveals a period of intense activity lasting some 15 to 20 msec. Figure 4 shows the recorded response with a microelectrode placed in the white column (A) and in the ventral horn of the gray substance (B). In each case the source of the excitation was a single shock to the column. The unmistakable localization of the burst of activity within the gray substance demands its origin from elements lying wholly within the gray substance. The elements contributing this burst must be Golgi type II cells constituting local or segmental interneuron pools. It is clear that the local interneuron pools are thrown into activity by the action of descending column fibers.

On repetition of the ventral column shocks, the activity within the local interneuron pool referable to subsequent shocks is facilitated during the first few msec., but it suffers occlusion and shortening thereafter. Figure 5 demonstrates this fractionation or channeling process in the interneuron pools accessible to column impulses. Three similar shocks were applied to the columns of the lower thoracic cord. The responses of the gray substance to these shocks in isolation are seen in Fig. 5 (A, B, and D). Figure 5C, in which two shocks fall in succession, shows the greatly synchronized response elicited by the second shock in comparison with its response in isolation seen in 5B. Figure 5E shows the response to a third shock similarly affected. By virtue of the channeling effect of combined facilitation and occlusion the actual internuncial response

to three successive column shocks, seen in 5E, is qualitatively very different from that calculated by the simple addition of the isolated responses 5 (A, B, and D). If the discharge and facilitation of the motoneurons is referable to these interneuron pools, then the qualitative changes described here should be reflected by the motoneurons. As is shown below in Fig. 12, this is the case. Hence it may be said that the internuncial impulses initiated by the descending column fibers, in turn impinge upon the motoneurons.

Figure 6 is a diagrammatic representation of the intermediate spinal mechanism through which long reflexes, occupying alpha-tempo fibres, must act on motoneurons. The connections established between fibres of the ventrolateral columns, the segmental interneuron pools, and the motoneurons are

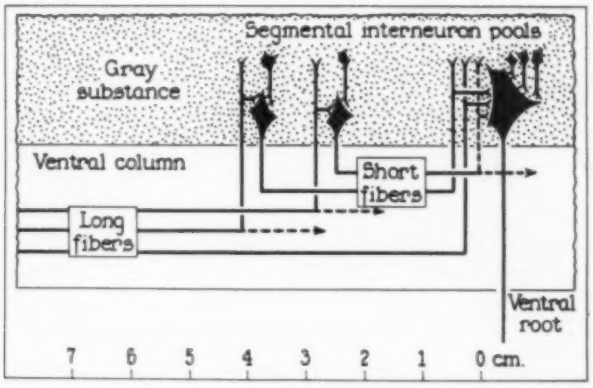

FIG. 6. Diagram of the pathways connecting the neurons of the ventrolateral column among themselves and with the motoneurons. Functionally the descending column system may be divided into groups of long and short fibers. The scale at the bottom indicates the approximate distance in centimeters of structures relative to the ventral root. For instance, the somata of the dominant short propriospinal neurons lie about 3 to 4 cm. cranial to the segment. The segmental interneuron pools are represented only by the final members of the chains. Paths indicated by broken lines are probable, but unproven.

shown. The pattern of the intermediate spinal mechanism as represented appears to be repeated at various levels of the cord, the position of any particular complex being a function of the position of a selected ventral root. All of the experiments to be discussed subsequently have been performed with conduction distances greater than the critical length of approximately 4 to 5 cm., and hence involve mediation of activity by the intermediate spinal mechanism as defined by Fig. 6.

Response of cord and motoneurons to a second tract shock

A single shock to the ventral column bundles discharges motoneurons either following the delivery of impulses relayed through the short propriospinal neurons, as in Fig. 3 (A and B), or after one or more additional

relays in the local interneuron pools. This is seen by comparing motoneuron latency in 7A (upper) with the time of the tract spikes recorded from the same segment in 7A (lower). The motoneuron discharge once instituted may last throughout the period of internuncial barrage.

On repetition of the ventral column shock, the short propriospinal impulses are increased by facilitation, as in 7 (C to H), lower records. These

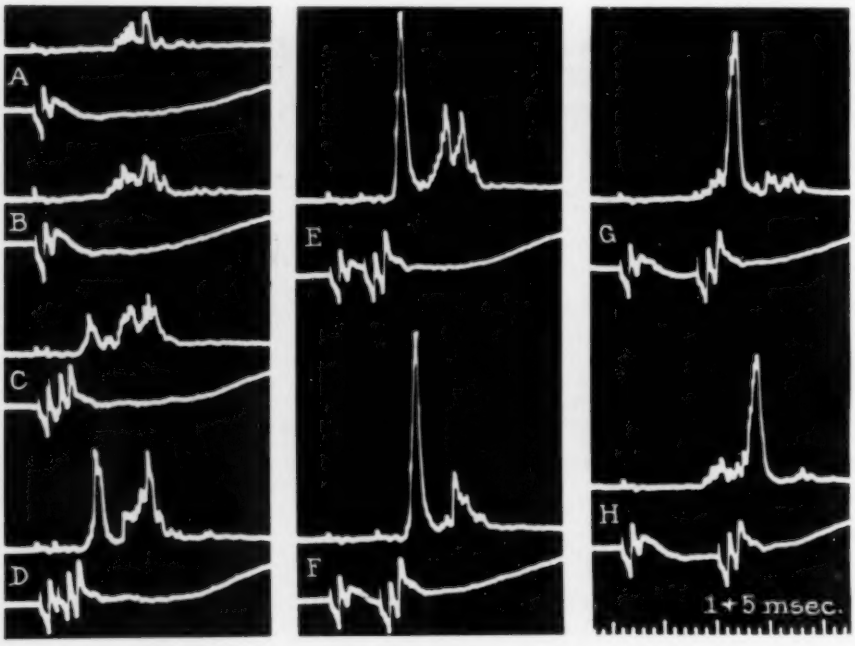

FIG. 7. Thoracolumbar preparation. Upper record in each of A to H is obtained from the 7th lumbar ventral root, lower record by microelectrode from the 7th lumbar segment. Cord conduction, 8 cm. A, response to a single column shock; B, to two shocks delivered simultaneously; C to H, to two shocks delivered serially at increasing intervals. Note synchronized motoneuron discharges produced by channeling of the internuncial response, and rigidly controlled in time by the relay short propriospinal volley.

fortified short propriospinal impulses now converge with local internuncial impulses at the motoneurons, with the result that the motoneuron discharge is advanced to a point but one synaptic delay behind the short propriospinal volley, as in 7C. The stimulus interval in 7C is 1 msec., while the motoneuron discharge (upper record) is advanced 3 msec. measured from the time at which it occurs following the conditioning shock alone (7A, upper) to a point just after the short propriospinal spike potential set up by the second shock (7A, lower). The short propriospinal impulses deliver a strong sharply synchronized synaptic excitation to the motoneurons, in contrast to the local internuncial barrage, which is highly asynchronous. Short propriospinal impulses from a second shock, converging with local interneuron pool im-

pulses, select a discrete segment of the motoneuron discharge for facilitation, with the result that a sharply synchronized motoneuron volley is produced, whereas the increase in local internuncial activity effected in 7B, by 2 simultaneous shocks, merely fortifies the asynchronous motoneuron discharge. The local interneuron pool impulses from the two shocks partially summate at the motoneurons when the shocks are seriatim, but again the resulting increase in motoneuron activity from this source, as in 7B with

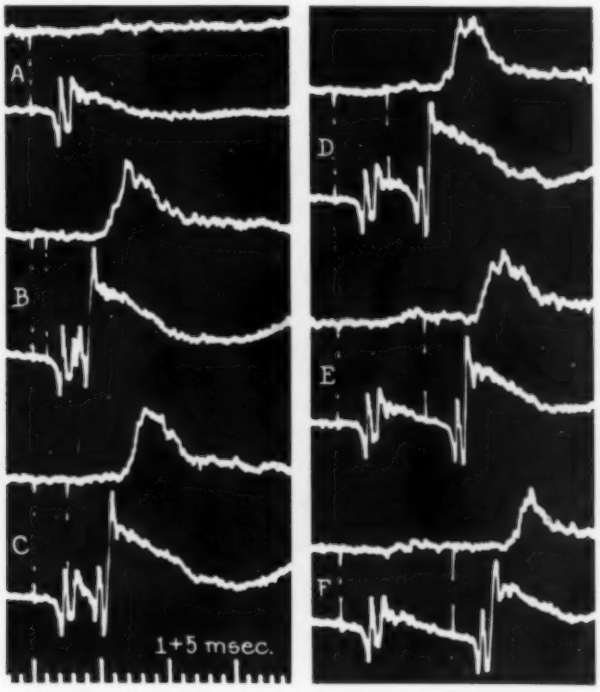

FIG. 8. Bulbosacral preparation. Cord conduction distance is 24.5 cm. Records from the 1st sacral ventral root above, and 1st sacral segment below, in each of A to F. Response to single shock to the floor of the fourth ventricle in A. B to F show responses to two similar shocks at increasing intervals. The onset of the facilitated motoneuron discharge is controlled in time by the short propriospinal volley.

simultaneous shocks, is much less intense and synchronous, as can be seen by noting the later motoneuron spikes in 7 (C to F). As the second shock falls still later (7, G and H), there is a marked decrease in the later motoneuron activity attributable to the second shock, although the facilitated synchronized volley is still in evidence. This decrease in motoneuron activity may be correlated with the occlusion of "cord potential" observable in the lower records of Fig. 7.

It may be noted now that the activity of local interneuron pools, as recorded by a microelectrode placed in the cord, manifests itself by a potential change of approximately 20 msec., during which period discrete spikes may

or may not be present. The prominence of spikes in such records is largely a matter of effective size of the recording microelectrode, the finer electrode favoring the recording of discrete spikes. The potential change, irrespective of electrical sign, is the analogue of the negative intermediary potential of Gasser and Graham (1933).

Figure 8 illustrates an experiment similar to that of Fig. 7. In this case, however, the shocks were delivered to the floor of the fourth ventricle. Records were obtained from the first sacral segment of the cord (lower records in each of 8, A to F) and the first sacral ventral root (upper records). A conduction distance of 24.5 cm. intervened. Practically no motoneuron discharge accompanies a single shock (8A, upper), although the cord record clearly reveals the direct and relayed spike potentials (8A, lower). With two shocks at various intervals (B to F), the relayed (propriospinal) impulses from the second shock are strongly facilitated, and as before with shorter conduction distance, they control the onset of the facilitated motoneuron discharge. With long conduction distance the higher multiple chains become relatively more effective, yet it is striking that the duration of the facilitated motoneuron discharge is not much more than doubled by the addition of 16.5 cm. of cord conduction.

The results of Fig. 8 emphasize the fact that the shortest effective pathway from the bulbar centers to the spinal motoneurons is through the propriospinal relay. It has not been possible to study the action of the long propriospinal fibers in isolation from the bulbospinal fibers. However, the essentially identical behavior of the system in Fig. 7, where a large portion of the fibers stimulated must be long propriospinal fibers, and in Fig. 8, where the long propriospinal fibers are certainly not stimulated, is strong evidence that the long propriospinal fibers play a part in relation to the spinal motoneurons more nearly like that of the bulbospinal fibers than that of the short propriospinal fibers.

Subliminal actions of ventral column volleys on motoneurons

It is possible to test the average excitability of a segmental population of motoneurons under any given set of circumstances by means of an ipsilateral dorsal root volley, while recording from the ventral root of the same segment (Renshaw, 1940). The first elevation of the reflex discharge set up by the dorsal root shock is mediated by arcs of two neurons, so that alterations in this elevation must reflect changes in the excitability of the motoneurons to synaptic stimulation, as a result of any chosen conditioning activity. In these experiments the conditioning activity is derived from shocks delivered to the ventral columns, or the floor of the fourth ventricle. The resulting alterations in the two-neuron arc reflex discharges demonstrate the subliminal changes associated with the motoneuron discharges described above.

Since with conduction distances greater than approximately 4 cm., the motoneuron discharge occurs only after the impulses of the short propriospinal relay impinge on the motoneurons, it is important to know whether

or not the long fibers mediating the direct spike potential volley of the cord record have synaptic connection with the motoneurons. Figure 9 illustrates an experiment designed to settle this question. A single shock was delivered to the ventral column bundles with the result shown in Fig. 9 (A and B). Figure 9B was recorded at 5 times the amplification used for the other records, to show details of the motoneuron response to the conditioning shock. A dorsal root volley in two-neuron arcs, 9C, was caused to impinge on the motoneurons during the latent period of the response to the conditioning activity, with the result seen in 9 (D to L). By following the amplitude of the initial reflex discharge elevation, marked with an arrow, it will be noted that a maximum is reached in 9G, after which comes a decrease, 9H, and a

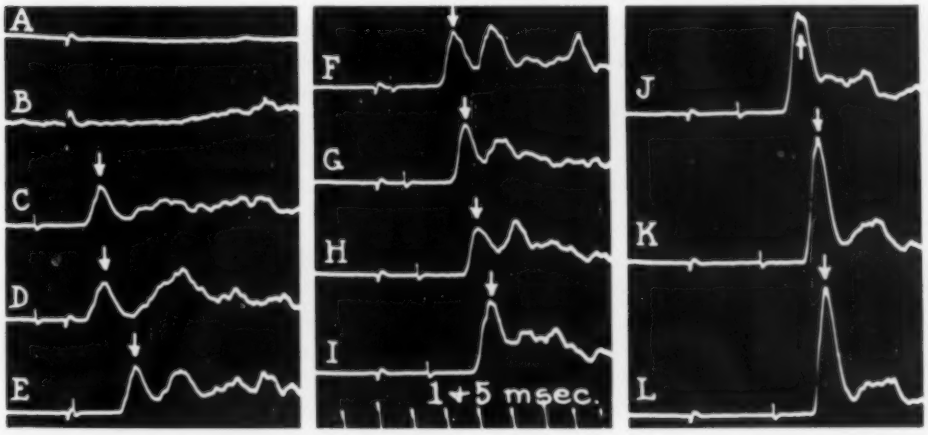

FIG. 9. Thoracolumbar preparation. Cord conduction distance, 8 cm. Records obtained from 7th lumbar ventral root show facilitation of two-neuron segmental reflex arc discharge by descending cord volleys. A and B, response to single conditioning column shock in isolation; B at 5 × amplification of other records; C, response to the dorsal root test shock in isolation; the discharge mediated through two neuron arcs is the elevation identified by an arrow. In D to L the dorsal root shock falls progressively later. Note the bimodal facilitation of the two-neuron arc discharge, the first maximum being reached in G.

second increase, 9 (I to L). This effect is best seen graphically, as in Fig. 10A in which many more separate observations could be included. In Fig. 10A the amplitude of the testing two-neuron reflex response is plotted as ordinate, against the interval between the conditioning ventral column shock and the testing dorsal root shock as abscissa. As demonstrated by Lorente de Nó (1935b), summation between impulses in different pathways at the motoneuron is maximal when the shocks are simultaneous, and has a total duration of less than 0.5 msec., given negligible conduction and equality of paths. Some divergence from these rigid criteria is inescapable in the present experiments, since there is a marked inequality of paths. In Fig. 9 and 10 the column conduction is 8 cm., the dorsal root conduction is 2 cm. Because these conduction paths are not only unequal, but in addition are relatively long, there will also be a degree of temporal dispersion of the detonator

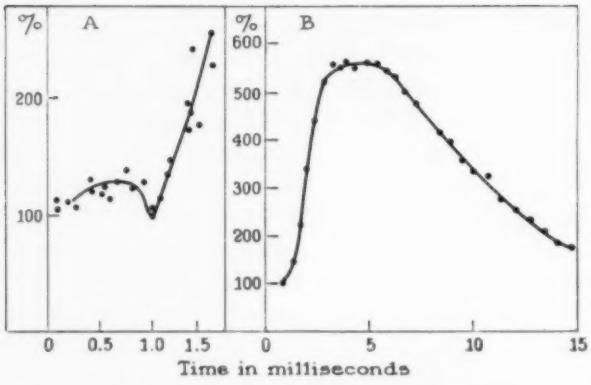

FIG. 10. Facilitation of motoneurons by a single column shock. Amplitude of the two-neuron arc response (ordinates) is plotted against the interval between conditioning column shock and testing dorsal root shock. Curve A presents detail of the early part of the facilitatory action of the column volleys and is constructed from observations, some of which are shown in Fig. 9. Curve B, the later course of the facilitation. Amplitude of the test response in isolation is 100 per cent.

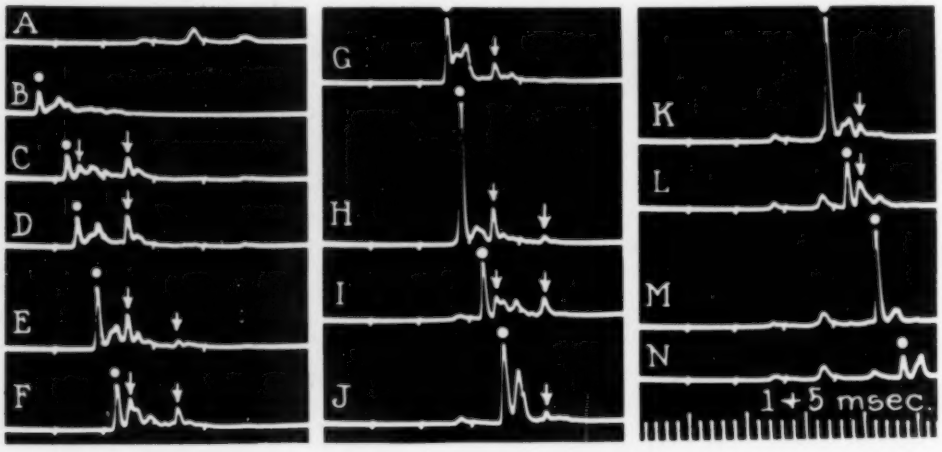

FIG. 11. Thoracolumbar preparation. Records from ventral root. Response of the motoneurons to four similar column shocks in succession shown in A; response to single dorsal root shock in B. The two-neuron arc elevation in B is identified by a dot. In C to N the dorsal root shock falls progressively later in the response to the four column shocks. The amplitude changes in the testing two-neuron arc discharge, marked throughout by a dot, reveal synchronization and augmentation of subliminal actions set up by the 2nd, 3rd, and 4th column shocks, which is not apparent following a single conditioning column shock (see Fig. 10B). Synchronization of subliminal actions on motoneurons parallels the synchronization of motoneuron discharges, both being due to channeling of activity through the shorter interneuron chains resulting from repetitive stimulation of the ventrolateral columns. Note also that the facilitated motoneuron discharge peaks resulting from convergence of later activity from the dorsal root shock with the column volleys and identified in the figure by arrows, are controlled in time by the direct column volleys, not the relayed short propriospinal volleys.

actions (Eccles) from both conditioning and testing sources. Given these somewhat unsatisfactory conditions, the fact that the first period of facilitation in Fig. 10A is distinct and has a total duration of less than 1 msec., is indisputable proof that long fibers do have synaptic connection with the motoneurons. The second rise in the facilitation curve, Fig. 10A, beginning in the 2nd msec., demonstrates the more powerful facilitating action of the short propriospinal relay impulses converging at the motoneurons. Subsequently facilitation progresses on a smoothly rising and falling course, 10B, which lasts during the period in which local internuncial activity is demonstrable, as in Fig. 4B, 5, and 7.

A correlation between the firing zone and the subliminal zone of a motoneuron pool can be shown under the conditions of repetitive excitation. Figure 11 presents records from an experiment in which the subliminal zone of the motoneuron pool is examined by means of changes in the two-neuron arc discharge as before. The response of the motoneurons to four similar column shocks in succession, seen in 11A, indicates directly the firing zone. The response to the testing dorsal root shock in isolation appears in 11B. In 11 (C to N) the test shock was caused to fall progressively later in the course of the response elicited by the conditioning column shocks. The two-neuron arc elevation is identified throughout by a dot. The course of facilitation, as indicated by amplitude changes of the two-neuron arc elevation, has four maxima, occurring in, E, H, K, and M. Each maximum occurs at the time of a motoneuron discharge in response to one of the four conditioning shocks.

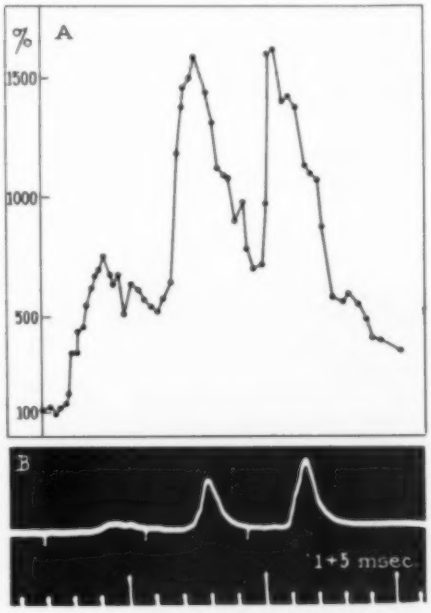

FIG. 12. Facilitation of motoneurons by three successive column shocks, the response to which in isolation is shown in B. Curve A plots the amplitude changes in the testing two-neuron arc volley as in Fig. 10. The course of the subliminal actions on motoneurons reflects the channeling of internuncial activity as recorded in Fig. 5. Frequency of stimulation for this effect is not critical, the only requirement being that subsequent shocks fall during the period of internuncial activity initiated by antecedent shocks.

Figure 12 shows a similar experiment in another preparation. A is a plot of the amplitude of the testing two-neuron arc response, and B shows, on the same time scale as used in the plot, the motoneuron response to the conditioning excitation, which is three shocks to the ventral column. As in Fig. 11, a peak of facilitation corresponds to each motoneuron discharge. The onset of each peak of facilitation is as rigidly fixed in time with respect to the causal shocks as is any known feature of synaptic activity. The form of

the action potential of the motoneuron discharge (12B) is determined by the number and temporal distribution of the motoneurons that are fired. After each added shock the number of motoneurons fired is increased and the firing occurs in greater synchronization, in exact accord with the prediction from the augmentation and synchronization of the internuncial activity that was described in connection with Fig. 5. In the corresponding facilitation curve (12A) it will be noted that the peaks change in form in a manner similar to that of the elevations in the motoneuron discharge record. They also become higher and shorter. Thus there can hardly be any doubt that the facilitation is caused by a bombardment of the motoneurons in the subliminal fringe by the same group of internuncial impulses that controls the supraliminal excitation.

Activity in dorsal and ventral interneuron pools in relation to effectiveness of column volleys

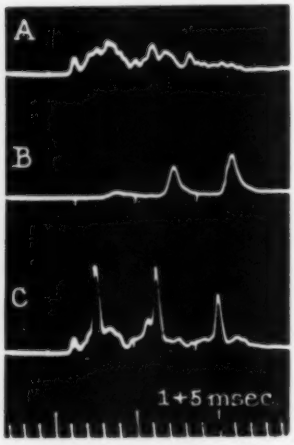

FIG. 13. Lumbar preparation. Conduction distance, 4.5 cm. A, motoneuron response to a single dorsal root volley. B, motoneuron response to three column shocks. The motoneuron discharge volleys in B follow the arrival of the short propriospinal relay impulses at the motoneurons. In C where the column shocks fall during the course of the response to the dorsal root shock, the direct column volleys control the time of the facilitated motoneuron discharge peaks.

It is a fact repeatedly confirmed that a volley of of impulses arriving at the motoneurons by the direct column fibers cannot effectively discharge these motoneurons, even if they converge with impulses from interneuron pools activated by other column volleys. On the other hand, when the same volley of impulses in the direct fibers converges with impulses from interneuron pools activated by a dorsal root shock, they are effective. Figure 13A shows the motoneuron response to a single dorsal root shock. Following the two-neuron arc elevation there is a random discharge lasting some 11 to 12 msec. Figure 13B shows the motoneuron response to three similar successive ventral column shocks. The three elevations of 13B appear following the arrival of the relayed column impulses in each case. In 13C the dorsal root and ventral column shocks are combined, with the result that three elevations, synchronized to 1 msec, or less, appear approximately 0.8 msec. in advance of the position of the corresponding elevations in 13B. In over 70 individual observations on this preparation no intermediate latencies were encountered. The control of the motoneuron response was advanced in a step-like manner from the relayed column (short propriospinal) impulses to the direct column impulses. Figure 11 shows the same effect in another experiment. The preparation in this case was narcotized with dial rather than decerebrated. The random discharge resulting from the single dorsal root volley lasted only 7 to 8 msec., as seen in 11B. As the

dorsal root shock is progressively delayed, 11 (C to L), it may be noted that sharply synchronized peaks appear out of the random reflex discharge as the latter encroaches upon the time of arrival of the successive direct column impulses at the motoneurons. These peaks are marked by arrows. The time at which these peaks appear is constant, being approximately 1 msec. in advance of the peaks elicited by the column shocks acting alone, and it is determined by the arrival of the direct column impulses. The absolute difference in latency between the observations of Fig. 11 and 13, approximately 1 msec., is occasioned by the different cord conduction distance used in the two experiments.

It is certain from anatomical studies (Cajal, 1909, Fig. 126) that separate interneuron pools are available to impulses from the tract fibers, and to impulses from dorsal root fibers. The former lie in the ventral horn region, the latter in the dorsal horn and the intermediate regions. Impulses from the ventral pools converging with the relayed tract impulses are effective, while those converging with the direct tract impulses are not effective. On the other hand, impulses from the dorsal pools converging with the direct tract impulses are able to excite motoneurons. This differential exciting power may result from a specific arrangement of synapses from the two groups of pools (see Lorente de Nó, 1938b), or it may merely indicate quantitative differences in their impulse output. At the present time there is neither the anatomical equipment nor an adequate differential measure of pool activity with which to carry reasoning further to a decisive answer.

Influence of other systems on propriospinal nuclei

The corticospinal system. Stimulation of the motor cortex conditions the discharge of propriospinal nuclei at various levels of the spinal cord; two examples are shown in Fig. 14. Figure 14A is the response of the cervical ventral column to a single shock delivered to the floor of the fourth ventricle. In 14B the floor shock is preceded by a train of 5 shocks delivered to the motor cortex. The direct spike potential of the column response is slightly increased, which may be interpreted as the result of summation at the reticular neurons of synaptic stimulation, mediated by corticobulbar fibers, and electrical stimulation by the floor shock (Lorente de Nó, 1935c). More prominent, however, is the facilitation of the relayed spike potential of the cervical short propriospinal neurons. Figure 14 (C, D, and E) demonstrates a similar effect of corticospinal activity on propriospinal neurons, the somata of which lie in the lumbar cord. Figure 14C shows the response of the lower lumbar cord to 5 shocks delivered to the motor cortex, while D is the response to a single shock applied to the ventral column of the upper lumbar cord. Under these experimental conditions the propriospinal relay must lie in the lumbar cord. Figure 14E, in which the lumbar cord shock is preceded by the motor cortex shocks, demonstrates that the response of the lumbar propriospinal neurons is facilitated.

The latency of the corticospinal effect is long, varying from 5 to 15 msec. by direct observation. One factor in the duration of the latent period is the remoteness of the spinal field chosen for study. In addition it is possible that the first detectable influence is exerted not directly, but indirectly through interneuron pools.

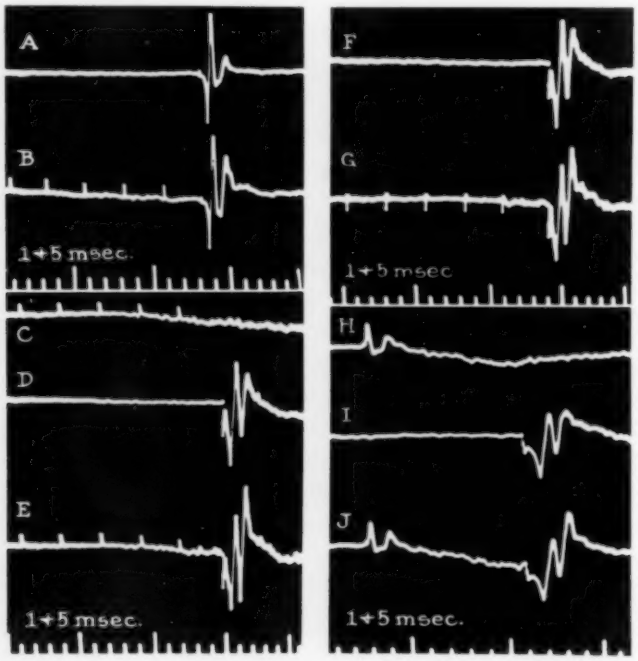

FIG. 14. A and B, bulbocervical preparation, A, response of the ventrolateral column of the cervical cord to a single shock to the floor of the fourth ventricle. In B, the propriospinal relay spike discharge of this response is facilitated by the action of 5 shocks delivered to the contralateral motor cortex, C, D, and E, lumbar preparation. C, response of the lumbar cord to 5 shocks delivered to the contralateral motor cortex. D, response of the lumbar cord to a column volley delivered to the upper lumbar region. In E, the lumbar propriospinal spike discharge is facilitated by the action of the cortical volleys. F and G, lumbar preparation. The propriospinal relay of the column response seen in isolation in F is facilitated in G by the action of 5 shocks applied to the central ends of cut strands of the brachial plexus. H, I, J, lumbrosacral preparation. H, response of the ventrolateral column to a single shock to the 5th lumbar root. Note that short propriospinal neurons are discharged by the dorsal root volley in H. In J, the discharge of the lumbosacral short propriospinal neurons is facilitated by the 5th dorsal root shock. I, column response in isolation.

Primary afferent systems. The influences of primary afferent neurons of the spinal region may be divided into two categories, which correspond to the long spinal reflexes and the short spinal reflexes of Sherrington (1898). Afferent neurons of the upper spinal field have an influence on lumbar propriospinal nuclei which, in its quantitative aspects, resembles that of the corticospinal system as noted above. Figure 14F is the response of the lower

lumbar cord to a single shock applied to the ventral column of the upper lumbar cord. This response is conditioned, in 14G, by 5 shocks delivered to the central end of strands of the severed brachial plexus, with the result that the spike potential of the lumbar propriospinal relay is facilitated. This effect on lumbar propriospinal neurons must involve at least the relay of activity through the long propriospinal neurons.

The results of stimulating primary afferent neurons, which supply the region of the short propriospinal relay itself, are somewhat different. The conditions for observing this situation were achieved in the experiment illustrated in Fig. 14 (H, I, and J) by placing the recording microelectrode in the first sacral segment and applying a ventral column shock 9 cm. orally. For conditioning, a single shock was delivered to the 5th lumbar dorsal root, the response to which is shown in 14H. Units of the propriospinal nuclei appear to be discharged directly by the dorsal root impulses, as shown by the presence of a relayed column spike potential following the dorsal root shock. Figure 14I shows the response to the testing ventral column shock in isolation. In Fig. 14J the ventral column shock is preceded by the 5th lumbar dorsal root shock, with the result that the discharge of the short propriospinal neurons is facilitated. A quantitative comparison may be drawn between the action of neighboring dorsal root fibers on short propriospinal nuclei, as in Fig. 14J, and the action of long propriospinal fibers on short propriospinal nuclei, as in Fig. 7H (lower record).

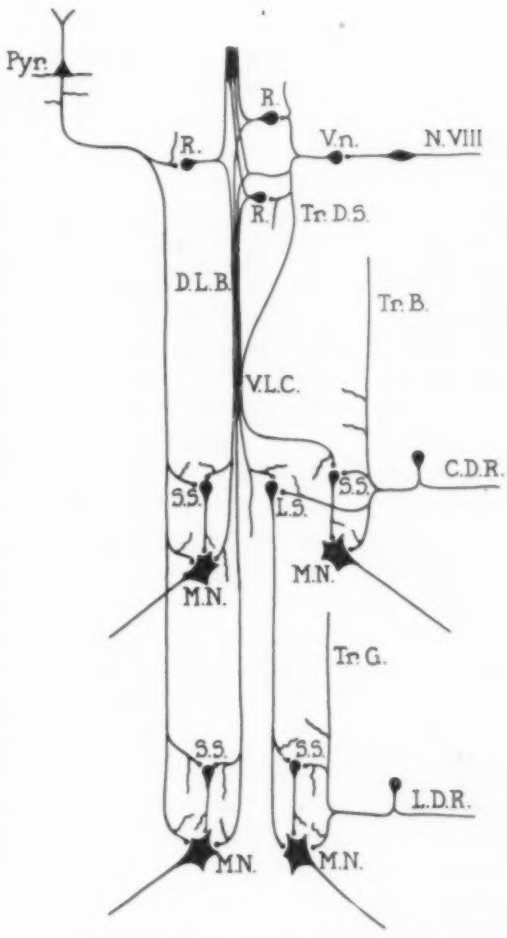

FIG. 15. Functional organization of unilateral connections of the bulbospinal correlation system. The connections of various primary afferent systems are given on the right-hand side. Connections from the contralateral motor cortex are on the left-hand side. C.D.R., cervical dorsal roots; D.L.B. dorsal longitudinal bundle; L.D.R., lumbar dorsal roots; L.S., long propriospinal neurons; M.N., motoneurons; N. VIII, vestibular nerve; Pyr., corticospinal neurons; R., cells of the reticular formation; S.S., short propriospinal neurons; Tr. B., tract of Brudach; Tr. D.S., vestibulospinal tract; Tr.G., tract of Goll; V.L.C., ventrolateral column; V.n., primary vestibular nuclei.

Functional organization of the correlation systems

Figure 15 serves as a diagrammatic survey of many of the foregoing observations and represents the functional organization of the correlation systems as they appear from the results of these experiments. It is admittedly incomplete and imperfect. Since no account has been taken of conduction across or up the spinal cord in these experiments, Fig. 15 includes only unilateral descending connections: the spinal pathways of least resistance (Sherrington, 1898).

It will be apparent from the foregoing experimental results that, with the exception of short spinal reflexes (Sherrington), all of the bulbospinal and descending spinal reflexes which employ the low threshold, rapidly conducting fibers, must involve two axially orientated neurons, one of which is a short propriospinal neuron. By comparing activity in the descending system with that of the ascending system to the oculomotor nuclei (Lorente de Nó, 1933–1939), it is clear that the propriospinal nuclei may be homologized with the reticular nuclei of the medulla, pons, and midbrain. Together the reticular and propriospinal nuclei form practically a continuous system of correlation centers influencing motoneurons from the oculomotor nuclei to the caudal spinal cord.

The correlation system is subjected to many external influences. The secondary vestibular fibers, for instance, are arranged so as to deliver impulses into the correlation system at all anatomical levels, through the dorsal longitudinal bundle, vestibulomesencephalic tract, and the vestibulospinal tract. Primary afferent systems other than vestibular send impulses into the system at their appropriate levels. The corticospinal system has been found to exert an influence at all levels. Although the vestibular and cortical influences enter the correlation system at all levels, this system must not be regarded simply as a collection of short fiber relays subservient to these influences at various levels; for within the system itself there are the long fibers of the reticulospinal tracts and of the long propriospinal tracts. The latter, by virtue of their demonstrated alpha conduction rate, must ensure the rapid diffusion of activity throughout the whole system. Thus it is possible that impulses in voluntary motor paths, through the known relays into the correlation system at the reticular formation, could assist in adjusting the posture of the whole animal to a state appropriate to the initiation of voluntary movement at the time of arrival of the voluntary motor impulses at the motoneurons.

Summary

The bulbospinal correlation system may be divided into two fiber groups, the long fibers represented by the reticulospinal tracts and long propriospinal tracts, and the short fibers represented by the short propriospinal tracts. Activity traverses the length of the neuraxis in the long fibers and enters the short propriospinal nuclei, apparently at all levels, to travel a short distance as relayed impulses along the short propriospinal fibers.

Impulses from the long fibers reach the spinal motoneurons directly and by the appropriate short propriospinal relays. These tract impulses also activate local interneuron pools of the ventral horn region, which in turn deliver impulses to the motoneurons.

In activity initiated from the upper cord and medulla the summation of impulses in the short propriospinal relays with local internuncial impulses from the ventral interneuron pools controls the time of firing of the earliest motoneuron volleys. The direct tract impulses, arriving at the motoneurons approximately 1 msec. earlier than the propriospinal relays, are ineffective. For the direct impulses to become effective the dorsal interneuron pools must be active. These dorsal interneuron pools are under the control of primary afferent neurons. When these pools are activated by a dorsal root volley, temporal control of the volleys in the motoneuron discharge passes from the relayed tract impulses to the direct tract impulses.

The total motoneuron discharge is in strict parallelism with the activity of intimately related interneuron pools. With repetitive volleys descending the cord, the internuncial activity is synchronized and augmented, and the activity so changed determines the size and duration of the motoneuron discharge. The subliminal fringe within the motoneuron pool varies with the discharge zone of that pool.

The propriospinal nuclei are subject to vestibular, reticular, corticospinal and primary afferent influences. They are, therefore, correlation centers in as true a sense as is the reticular formation.

The temporal exactitude with which discharges occur in the interneurons of the column tracts and in the motoneurons guided by these discharges, attests to the importance of timing as a factor in synaptic transmission in the spinal cord.

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